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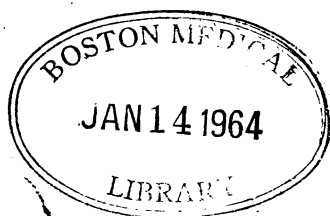
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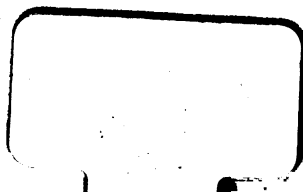
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PHYSIOLOGICAL PRINCIPLES
IN TREATMENT

LANGDON BROWN



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TREATMENT

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BY

W. LANGDON BROWN, M.D. CANTAB., F.R.C.P.

PHYSICIAN TO THE METROPOLITAN HOSPITAL; MEDICAL REGISTRAR AND DEMONSTRATOR OF
PHYSIOLOGY, ST. BARTHOLOMEW'S HOSPITAL



LONDON
BAILLIÈRE, TINDALL AND COX
8, HENRIETTA STREET, COVENT GARDEN
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PREFACE

IN the last decade our ideas have undergone fundamental alterations on many points of cardinal importance in physiology. The same period has seen a much wider use of exact scientific methods in clinical work. The result has been a closer harmony between physiology and practical medicine. The researches of Pawlow and his followers, which have led to the rewriting of the physiology of digestion, the clinical applications of Gaskell's work on the heart by Mackenzie and others, the introduction of convenient methods of registering blood-pressure in man, the increased knowledge of the chemistry of uric acid and its congeners, of nitrogenous metabolism and internal secretion, are examples which will occur to anyone.

The busy practitioner is aware that the physiology of his student days has been largely supplanted or supplemented, but has not time to acquaint himself with the changes, nor to deduce therefrom the points on which his clinical conceptions should be modified.

This book does not aim at being a complete treatise on applied physiology; but as it has been my lot during the decade in question to combine the practice of medicine with the teaching of physiology, I have set down here some of the considerations which I think have helped me, in the hope that they may help others.

Several chapters were originally delivered as lectures at the Polyclinic and elsewhere, and their reception in that form has encouraged me to hope that they may prove acceptable to a wider audience.

In a book of this kind it seemed unwise to burden the text with many references. At the end of the last chapter, however, I have given references to some easily accessible works in which bibliographies will be found, so that anyone interested in any special point can follow it up without difficulty.

I am indebted to my colleague, Dr. C. M. Hinds Howell, for kindly reading the proofs and giving me the advantage of his criticisms on several points. To my colleague, Dr. Leonard Williams, I owe many thanks for sound advice and practical suggestions.

Though the days are past when the student entering the wards often received the superfluous advice to 'forget his physiology,' the physiologist is still regarded a little suspiciously at the bedside. Perhaps he is in part himself to blame for that, for he is sometimes inclined to forget that observations made in the laboratory are not infallible, and are not necessarily more correct than clinical evidence. When I reflect that I am now teaching the exact opposite to many of the views held ten years ago, I feel that physiology can only come to the aid of medicine with becoming modesty, and without overweening dogmatism. There is no finality about either, but that they can co-operate usefully I trust the following pages serve to illustrate.

W. LANGDON BROWN.

37A, FINSBURY SQUARE, LONDON, E.C.

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CONTENTS

CHAPTER	PAGE
I. THE PRINCIPLES OF ORGANO-THERAPY - -	1
II. THE RATIONAL TREATMENT OF GASTRIC DISORDERS -	44
III. THE WORK OF THE PANCREAS - - -	91
IV. URIC ACID AND THE PURIN BODIES - -	123
V. OXALURIA, PHOSPHATURIA, AND ALBUMINURIA -	139
VI. GLYCOSURIA AND DIABETES - - -	169
VII. ACETONURIA AND ACID INTOXICATIONS -	188
VIII. INTESTINAL INTOXICATIONS - - -	214
IX. IRREGULAR ACTION OF THE HEART - -	241
X. THE VASOMOTOR SYSTEM IN DISEASE - -	269
XI. ON CYANOSIS - - - -	300
XII. THE RÔLE OF CALCIUM IN THE BODY - -	314
REFERENCES - - - -	333

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PHYSIOLOGICAL PRINCIPLES IN TREATMENT

CHAPTER I

THE PRINCIPLES OF ORGANO-THERAPY

WHENEVER we give a drug, we imply thereby a belief that the functions of the body can be influenced by chemical means. And we can find support for this confidence in the fact that the body itself produces chemical substances whereby it regulates its own functions.

Nothing could be more reasonable than to use intelligently in disease those very drugs by which the body is enabled to do its own work in health. This is the basis of a rational organo-therapy, as Starling has so clearly indicated.

Though the use of organic extracts has enormously increased during the last decade, it is but the renaissance of a very ancient method. Celsus and Galen testify to the antiquity of organo-therapy. The first Pharmacopœia, published by the College of

Physicians in 1618, contains several preparations of animal extracts.

The success of thyroid extract in treatment led to a great revival of interest in the subject, an interest not always intelligently displayed. Indiscriminate use of gland extracts in every sort of disease, without consideration of the underlying principles, only brings discredit on a valuable method of treatment. There is no scientific sanction for the employment of brain extract in insanity, and extracts of bronchial glands for phthisis. Powdered heart muscle was a favourite prescription in the old days; it is no advance to squeeze it into a tablet and call it cardin.

In the past it has been too much the fashion to look upon the different organs as largely independent of each other, though under the suzerainty of the brain. But the development of a nervous system is a comparatively late event in evolution. The stimuli to which the most primitive forms of life respond are chemical; the nervous system enables very rapid reactions to occur, but where less sudden responses are needed the primitive method is retained.

Thus, salivary secretion may occur before the food enters the mouth; and though gastric secretion is started by the taste of the food, its continuance is due to chemical stimuli, while pancreatic secretion can be explained by chemical factors alone. Here we note a gradual transition from a nervous to a chemical method of stimulation, as the need for rapidity of response grows less. This is a good

example of the way in which the nervous system may start a series of events, though the subsequent chapters are due to chemical interactions, one organ producing a chemical substance necessary as a stimulant to the next in series.

For these substances Starling suggests the name 'hormones' (*ὁρμαω*, 'I excite'). Internal secretions are simply examples of more widely distributed hormones. The following table (slightly modified from Starling) gives some of the more recognised of these:

Origin.	Hormone.	Reacting Organ.
Suprarenals.	Adrenalin.	Sympathetic nervous system.
Stomach (pylorus).	Gastric secretin.	Stomach (fundus).
Duodenum.	Secretin.	{ Pancreas.
Pancreas.	Pancreatic juice.	{ Liver.
Thyroid.	Iodothyrim.	Intestine.
Ovaries.	...	Nervous system, skin, etc.
Fœtus.	...	Uterine mucous membrane.
		Mammary gland.

This list could probably be extended; it is, indeed, difficult to decide where the line should be drawn, for the chemical products of every organ must influence the rest of the body to some extent. But it is only when that influence is specific that we dignify the chemical product with the status of a hormone. Thus, carbon dioxide is a product of all the tissues, but has a specially stimulating effect on the respiratory centre, while kreatin, which is formed by muscular

tissues, increases the excitability of motor nerve endings. Such reactions differ in degree rather than in kind from those of iodothylin and adrenalin.

Abrahams classified thus the inherent apparatus by which the body can defend itself when attacked :

1. *The physiological reserve*, primarily to combat exhaustion. This is called up in any condition of unusual strain, cardiac hypertrophy being a typical example.

2. *The biochemical apparatus*, which enables one tissue, when attacked, to appeal to another for assistance.

3. *The nervous mechanism*, which, as we have seen, is the latest in evolution, and the swiftest and most complex in its action.

The most essentially vital acts are subserved by a double mechanism. Thus, in heart diseases it is to the physiological reserve and the nervous mechanism that we look, while in digestive disturbances we must rely on the biochemical apparatus and the nervous system. In organo-therapy we are calling the biochemical apparatus to our aid.

Now, the substances which produce effects upon the body fall into two groups (Ehrlich). The first are closely allied in their chemical character to proteins, such as the toxins; all are produced by the agency of living organisms. As a result of their introduction, the tissues react by development of an antibody. The second group include all the common drugs, which probably act on protoplasm by reason of

their molecular configuration, producing their effect, without any incubation period, as soon as they reach the cells. Although repeated doses can set up a certain degree of tolerance, they never give rise to the production of an antibody.

We should expect hormones to belong to the second class, because if they excited the production of an antibody, larger and larger doses would be required to effect their physiological purpose, which would defeat their own object. In other words, they belong to the permanent, and not to the acquired, defences of the body.

The general features of hormones may be stated thus :

1. They are bodies of comparatively small molecular weight.

2. Unlike ferments, they are not destroyed by simple heating, but may lose power on prolonged boiling.

3. They are rapidly destroyed by oxidizing agents.

4. They are destroyed in the tissues which they excite, and do not escape in any of the excretions.

5. They are not, as a rule, absorbed unaltered from the alimentary canal. Iodothyryn, the active principle of thyroid extract, is an exception to this rule, probably because the thyroid gland originally discharged its secretion into the alimentary canal by the thyro-glossal duct.

From the practical point of view we may note especially—

1. That, so far, we can usually employ typical hormones only by local application or injection.

2. That as they can be added to boiling water without loss of strength, the question of sterilization is much simplified.

3. That as they disappear, probably by oxidation in the tissue they excite, they are more useful in producing sudden than prolonged effects.

It will be convenient to consider in turn the chief hormones which have been employed in therapeutics.

The Thyroid Gland and Iodothyrim.

Organo-therapy won its first and most conspicuous triumph in treatment by thyroid extract. The ease with which thyroid preparations are absorbed from the alimentary canal has greatly contributed to this, but at the outset it was not realized that so simple a method would be effective, and subcutaneous injections were employed.

The only active principle that has been isolated from the gland is iodothyrim, a substance rich in iodine and nitrogen, prepared from the colloid in the vesicles by artificial digestion. Whether this is the only active substance in the gland has been doubted; Schiff found that its effect upon metabolism was less marked than that of an extract of the whole gland. The presence of iodine, which is a striking peculiarity in this hormone, is specially interesting in view of the empirical use of iodine in diseases of the thyroid.

But the iodine in the gland seems to vary in amount in different animals, and appears to be absent altogether in cattle.

From its great success in myxœdema and cretinism, we may regard iodothyrim as a hormone having a specific action on the central nervous system and on the skin and subcutaneous tissue. I do not propose to dwell on these points, which are familiar to all. The occasional failures in the treatment of myxœdema may be explained thus :

1. In persons of advancing years iodothyrim appears to have less effect.

2. As subjects of myxœdema are more liable to those toxic symptoms known as thyroidism, it is not always possible to give an adequate dose.

While failures in the treatment of cretinism may be accounted for thus :

1. Successful treatment is only possible before the degeneration of the brain consequent on cretinism has occurred.

2. Errors in diagnosis have led to Mongolian idiots and achondroplasics being treated as cretins.

The effect of iodothyrim on metabolism is that it reduces weight, only one-sixth of the loss being due to increased nitrogenous waste, the remainder being due simply to the diuresis it causes, apparently by dehydration of the fats. It may produce glycosuria. It accelerates the heart-beat without augmenting its force. It is therefore not very effective in the treatment of obesity, and its use is not free from risk, as

a fatty heart may not be able to maintain the accelerated rhythm. Moreover, as in obesity there is often latent glycosuria, the use of a drug which can develop that latent into actual glycosuria is distinctly inadvisable.

Among the less-known effects of iodothyron on metabolism is its influence on the liver. Apart from the discoloration, the chief sufferings of a jaundiced patient are due to the toxic effects of the bile-salts; prominent among these is the intense itching, which is sometimes so troublesome.

Now, it has been found that after ligature of the bile-duct there is an increase of colloid in the follicles and lymphatics of the thyroid gland. It appeared possible that this was a defensive step against intoxication by bile-salts, and accordingly Gilbert and Herscher administered thyroid extract to seven cases of jaundice; in six the pruritus was benefited.

Under thyroid treatment the bile-salts in the urine gradually diminished and then disappeared. After cessation of treatment the reaction returned until thyroid extract was again administered. They concluded that thyroid extract must modify or destroy the bile-salts. Outside the body they did not find that thyroid has any effect on bile-salts.

Employing Grünbaum's method of estimating bile-salts, I have been able in several cases to confirm Gilbert and Herscher's statement that the administration of thyroid extract diminished the amount of bile-salts in the urine with great relief of pruritus.

I found, on keeping urine with a known amount of bile-salts at the body temperature and comparing it with a similar mixture to which I had added iodothyron, that the iodothyron did not destroy a perceptible amount of bile-salts, though a small amount did disappear on prolonged heating in a water-bath. Similarly, iodothyron had no destructive effect on bile-salts added to blood even after incubation for twenty-four hours.

Evidently one must look to the liver itself for an explanation; is it possible that iodothyron inhibits the formation of bile-salts by the liver? To test this I gave a cat weighing 7 pounds iodothyron and sometimes elixir of thyroid with its food for a week; under chloroform and ether a cannula was introduced into the gall-bladder, the common bile-duct clamped, and the bile collected for an hour, during which time seven injections of bile-free secretin were given to stimulate the flow of bile. The bile-salts were then estimated, and found to amount to 0.026 gramme. In a control cat weighing 6 pounds 2 ounces, which had had a similar diet without iodothyron, 0.067 gramme was secreted under similar conditions in an hour. This strongly suggests that iodothyron positively diminishes the formation of bile-salts, and provides us with a rational method of diminishing the disagreeable symptoms in jaundice due to their presence in the circulation.

The striking changes occurring in the skin in myxoedema implies that iodothyron plays an important part in regulating its nutrition. Byrom

Bramwell therefore employed thyroid extract in various diseases of the skin. The best results seem to have been obtained in psoriasis, ichthyosis, and lupus vulgaris. Its use should be restricted to chronic conditions; Radcliffe Crocker finds that it may excite new lesions if given while the eruption of psoriasis is still developing.

As fractures have been found to heal better in thyroidectomized animals if thyroid extract be given, it has been used to hasten the union of fractures in normal individuals, apparently with benefit.

In eclampsia thyroid extract has been advocated, on the ground that in normal pregnancy an enlargement of the thyroid gland occurs, while in the albuminuria of pregnancy or in eclampsia this enlargement may be lacking. As we have seen, some effect on hepatic metabolism must be conceded to the thyroid, and it is to some hepatic lesion that we must look for the explanation of eclampsia. There is, therefore, a rational basis for this plan of treatment, though it is possible that all the benefits observed can be referred to the diuretic action of the iodothyrim.

Since tetany has been observed after excision of the thyroids and parathyroids in animals, thyroid extract has been employed in its treatment. Tetany may occur after prolonged lactation, and it is quite possible that this is due to the drain of iodothyrim into the milk. At any rate, an infant may develop thyroidism if the mother is taking thyroid extract, so that the drug evidently passes into the milk with ease.

It is not possible to make a positive statement at present as to the alleged value of thyroid medication in cancer of the breast.

Much has been written concerning the function of the parathyroids, and it has been asserted that the twitchings and spasms which have been observed in experimental extirpation of the thyroid, but not in myxœdema, are due to the removal of the parathyroids in the former case, while they are believed to escape in the latter. But it is very difficult to accept this, in view of the careful observations of Forsyth on the parathyroids (*Quart. Journ. of Med.*, vol. i., p. 150). As a rule these small bodies cannot be detected with certainty by the naked eye; they occur in positions other than those generally recognised; they are more numerous than is commonly supposed; they are not infrequently attached to lymphatic glands, thymic residues, or accessory thyroids; they may be microscopic in size, and, finally, they may be deeply buried in the substance of the gland. To remove them completely must, therefore, be almost impossible. Forsyth concludes that the parathyroids are portions of the main thyroid glands which have assumed functional activity, but have not yet formed vesicles. All intermediate stages between thyroid and parathyroid tissue occur. The parathyroids must therefore be regarded as essentially the same in function as the thyroid. There is no satisfactory evidence that the parathyroids bear a pathogenic relationship to any known disease.

The striking contrast between Graves' disease and myxœdema naturally suggests that while the latter is due to an athyrea, the former is due to a hyperthyrea. In Graves' disease the gland is enlarged by an increase in the secreting cells, the excitability of the nervous system is increased, the pulse is rapid, the temperature is raised, the skin is moist, the consumption of oxygen is increased, and there is usually emaciation. In myxœdema the gland is atrophic, the excitability of the nervous system is diminished, the pulse is slow, the temperature subnormal, the skin dry, while diminished oxygen consumption and increase of weight is the rule. Moreover, the administration of excessive doses of thyroid extract may cause symptoms analogous to those of Graves' disease. If iodothylin is a hormone acting on the skin and nervous system, Graves' disease can be most readily explained by a hyperthyrea in which the emotional centres undergo an excessive stimulation. Hector Mackenzie has drawn attention to the resemblance between the symptoms of Graves' disease and the expression of the emotion of fear. In both we have the staring eyes, the rapid pulse, and the tremors. It is doubtful, however, whether all the phenomena of Graves' disease can be explained by hyperthyrea alone. Myxœdema following Graves' disease we can understand on this hypothesis, for the gland may become exhausted as a direct result of its excessive activity; but the coexistence of active Graves' disease with some of the symptoms of myxœdema,

such as the characteristic condition of the skin, is very difficult to account for. But such cases undoubtedly occur. To say that Graves' disease is due to a perverted rather than an excessive secretion of the thyroid does not carry us much further.

Organo-therapeutic measures in Graves' disease have not been an unqualified success, which is hardly surprising, as we do not really understand the line along which success should be looked for. Thus, if the essence of the disease is a hyperthyrea, administration of thyroid extract could do nothing but harm. Yet some observers have reported a positive benefit from its use.

The other organo-therapeutic lines of treatment that have been tried are antitoxic and cytolytic. The hypothesis on which the former method rests is that the blood of a thyroidectomized animal should contain an excess of substances unneutralized by thyroid secretion; these should be antagonistic to a hypertrophied thyroid. But the proof that such substances occur is not satisfactory, and the hypothesis implies an antitoxic rather than a secretory function for the thyroid.

Rodagen (a dried preparation from the milk of thyroidectomized goats, with an equal weight of milk-sugar to preserve it) has been advocated. It is given in doses of 1 to 3 drachms a day. As the wholesale price is 3s. to 4s. an ounce, such a treatment is decidedly expensive. Hector Mackenzie concludes that it seems to do some good, though the

results have not been very striking. Lately Edmunds has reported benefit from the use of the fresh milk of thyroidectomized goats. Antithyroidin is a preparation of the serum of thyroidectomized rams, the glands having been removed six weeks previous to the first bleeding. It may be given by mouth, hypodermically, or *per rectum*. It is claimed as a remedy that has been tested, 'but found wanting,' Hector Mackenzie adds. It is even more expensive than rodagen, the average daily dose costing 2s. 6d.

Thyroidectin is a similar preparation, but much cheaper, the average daily dose costing about 4d. I have noted improvement following 5-grain doses three times a day, but I am not sure that the improvement was more than has been observed under more ordinary lines of treatment.

The trial of thyrolytic serum is based on the well-known fact that if a preparation of the cells of one animal be repeatedly injected into the circulation or peritoneal cavity of another animal, the latter will form an antibody capable of destroying those introduced cells. To prepare a satisfactory thyrolytic serum for human thyroids, it might be expected that an emulsion of human thyroids must be employed for the injections. In the analogous case of precipitins, the antibody prepared against dog's blood, for instance, has no effect on ox's blood. This consideration does not appear to have always been borne in mind. But another and much graver objection must be raised. A serum that will destroy the cells of the

thyroid gland in an animal will also destroy the cells of other organs, such as the liver or kidney. In other words, cytolytic sera are not specific for the same organ in different animals, but for all the cells of a particular animal. The treatment is, therefore, at once ineffective and risky.

If there is anything in the antitoxic hypothesis, it is inadvisable, as H. Mackenzie points out, to give milk and meat from animals in full thyroid activity to patients taking preparations from thyroidectomized animals. The two would tend to counteract each other. Moreover, Chalmers Watson has described hypertrophy of the thyroid as occurring in animals on an excessive meat diet. A reasonable diet in Graves' disease would be fish, chicken, fat bacon, eggs, vegetables, salad and fruit, cream, butter, bread, and carbohydrates generally.

The Suprarenal Capsules and Adrenalin.

Following on Addison's clinical observations, Brown-Séquard showed that experimental removal of the suprarenals was rapidly fatal to animals. This he regarded as the result of the accumulation of some toxic substance which it was the function of the suprarenals to destroy. This antitoxic view of their action was commonly held until Schäfer and Oliver in 1893 prepared from them an active substance possessed of powerful tonic properties. That this substance was only formed from the medulla of the

gland was shown by Swale Vincent from observations on certain fishes in which the cortical and medullary portions form separate glands. Attempts to isolate the active principle from the extract culminated in 1901 in the preparation by Takamine of a crystalline body, to which he gave the name of adrenalin, and to which he attributed the formula $C_{10}H_{15}NO_3$.

Four years later Dakin synthesized it artificially from pyrocatechin, and made a series of similar bodies, showing that their activity depended on the presence of a catechol nucleus. This suggests an origin from the aromatic radicles present in the protein molecule. Its formation in the medulla of the suprarenal is of great interest when we remember that this portion of the gland is developed as a direct outgrowth from the sympathetic nervous system. Nor is this the only example of such an association, for sympathetic paranglia and structures, such as the carotid body, contain *paragangline*, a similar but more stable body, which does not lose its effect even if left in contact with the stomach wall for twenty-four hours.

We owe to Langley the important generalization that the action of adrenalin on any part is the same as stimulation of the sympathetic nerves to that part. It will not act on a structure that at no time in its history has been innervated by the sympathetic. Elliott, in extending these observations, has brought forward some facts which suggest that, after excision of the suprarenals, the muscles innervated by the sympathetic cannot be thrown into activity even

by electrical stimulation of the nerves. Adrenalin appears, then, to be a chemical body whose presence is essential to the activity of the sympathetic. This is doubly interesting in view of its formation by a structure of sympathetic origin.

In applying adrenalin therapeutically we have to consider what would be the effect of stimulating the sympathetic nerves to the part in question. Whether it acts on a 'myoneural junction,' as suggested by Elliott, or on a 'receptive substance' in the cell, as Langley thinks, does not affect this conclusion. The application of adrenalin to internal medication is greatly limited by two facts:

1. If mixed with alkalies, its activity is lost; if the alkali is neutralized, the specific effect can be obtained again. Now, as the blood-stream is alkaline, it is difficult to see how it can produce a general effect through the circulation.

2. It is doubtful whether in healthy persons it is absorbed unaltered from the alimentary canal. The most striking action of adrenalin is the rise of blood-pressure that it causes, but many observers have failed to detect any rise when the drug has been given by the mouth. Yet it is not destroyed by gastric juice in a test-tube. Probably the intense vaso-constriction it produces prevents its own absorption. Rolleston found that, given by the mouth to persons suffering from Addison's disease, it did raise the blood-pressure, and on this a diagnostic test for Addison's disease has been based. In the same way

a myxœdematous person is well known to be much more sensitive to thyroid extract than a healthy individual. Schäfer thinks that injured vessels are similarly more sensitive to adrenalin than normal ones, and that a selective vascular constriction may be thus produced even though no general rise of blood-pressure occurs.

It will follow that the drug is most effective when it can be applied direct to the point at which we wish it to act. Even after subcutaneous injection its general effect is much interfered with by the local constriction of bloodvessels, which prevents its passing into the circulation until its activity has passed off.

Alimentary Canal.—Since Grünbaum suggested suprarenal extract for hæmatemesis, many instances of its successful use have been reported. I have come to place great reliance on $\frac{1}{2}$ -drachm doses of the 1 in 1,000 solution of adrenalin chloride in $\frac{1}{2}$ ounce of water, given every three or four hours. In addition to constricting the bleeding-point, it stops peristalsis. If an isolated loop of intestine be placed in a bath of warm salt solution, vigorous peristaltic waves may be seen; the addition of two or three drops of adrenalin solution to the bath at once renders the coil quiescent. Like the sympathetic, adrenalin inhibits the movement of a hollow viscus, while keeping the sphincter controlling the exit closed. Herein lies its advantage over ergotin and the like. For these reasons it will often check vomiting, in doses of 10 minims of the 1 in 1,000 solution diluted with water.

It should be tried in intestinal hæmorrhage, though it is open to doubt whether the drug can get past the pyloric sphincter. Graeser succeeded in checking severe intestinal bleeding in typhoid fever by giving three hourly doses of 30 minims of the solution by mouth where ice, opium, ergot, and bismuth had all failed. I have been using it in this way for several years, and have been satisfied with the results. It may be added also to an enema of starch and opium.

As a precautionary measure I am accustomed to give a similar dose about a quarter of an hour before getting the bowels opened by enema after an intestinal hæmorrhage. By keeping the bloodvessels of the small intestine constricted, the walls flaccid, and the ileo-cæcal sphincter closed, it affords the ideal condition for emptying the large bowel by enema.

Adrenalin has been recommended for gastro-intestinal atony; but in view of its inhibitory action on peristalsis, it is difficult to believe that it could be of service.

Exner found that intraperitoneal injection of adrenalin delays the absorption of poison introduced into the stomach or peritoneal cavity; thus strychnine required twenty times as long to produce its toxic effect. This gain of time is most valuable, and suggests the administration of a full dose of adrenalin pending the employment of other remedies.

Heart and Bloodvessels.—Adrenalin is a powerful stimulant to the heart, augmenting its action like the sympathetic; but, as we have seen, to produce this

effect it must be injected intravenously. We must remember, however, that as it also constricts the bloodvessels, thereby raising the pressure, it may stimulate the cardio-inhibitory centre in the medulla, so that slowing of the heart through the vagi might be caused instead. Though this might perhaps be prevented by simultaneous injection of atropin, this would merely mean that a way of escape from the excessive pressure would be barred. The sudden vaso-constriction greatly increases the work of the heart, and if this cannot be met, dilatation of the cavities may occur. Dilatation and vagal inhibition are dangers that would outweigh any advantage to be derived from the stimulating effect of the adrenalin. The safest thing to do is to give amyl nitrite at the same time, unless the blood-pressure is already low ; this will flush the peripheral vessels, thus avoiding the extra work and the stimulation of the cardio-inhibitory centre, though not entirely eliminating the rise of pressure. The action of both drugs is about equally sudden and transitory. I regard 10 minims as the maximum dose that should be employed intravenously at one time. Fortunately, it has been shown experimentally that adrenalin does not constrict the coronary vessels, for if it did it would almost certainly produce anginal attacks. In cases of shock, where the blood-pressure is lowered from dilatation of the splanchnic bloodvessels, adrenalin is free from these risks, so that the amyl nitrite is unnecessary. And it is becoming more recognised that many cases

of 'heart failure' in toxic states are really due to vasomotor paralysis, so that there is a considerable field of usefulness for adrenalin in such cases, if its mode of action is duly borne in mind. I have seen great improvement follow intravenous injections for the collapse of toxæmic states, especially pneumonia, as Rolleston has found. Elliott and Tuckett's observation that in one toxæmic condition, diphtheria, the chromogen in the medulla is deficient may afford an explanation of these facts. Crile showed experimentally that in the most profound shock it was possible to keep up the blood-pressure and maintain life by the continuous intravenous infusion of adrenalin in salt solution, 1 in 50,000 to 100,000. In the collapse of chloroform or opium poisoning it has also been found useful, though Schäfer has not found it possible to revive the cardiac muscle permanently in this way.

Butler has recorded a striking example of its success in an attack of syncope after the crisis of pneumonia in a child of ten. He injected 38 minims in all in five doses, besides giving 10 minims by mouth. He says: 'No words of mine can express the absolutely marvellous nature of the change in the child's condition due to the drug.' He reports a very significant fact, however: 'Each time it was noticed what was most apparent after the initial large injection—namely, that the immediate effect was an increase of pallor and a weakening of the pulse, followed by great and rapid improvement.' Evidently, in the

doses here used the immediate rise of blood-pressure was enough to act on the cardio-inhibitory centre in the way I have pointed out.

In accordance with the general law that adrenalin only acts on structures which have a sympathetic innervation, it is interesting to note that Baum found it had no effect in blanching nævi, and only a very transitory effect on unsound flesh.

Adrenalin in Hæmoptysis.—In the chapter on the Vasomotor System in Disease, it is pointed out that the changes in the pulmonary circulation are passive, and are controlled by the systemic circulation. On perfusion of adrenalin through the pulmonary vessels Brodie and Dixon could not find any evidence of vaso-constrictors, though Plumier obtained a positive result from larger doses. At any rate, the effect is not nearly so marked as on the systemic vessels. I have seen the thoracic viscera from an animal killed by a fatal dose of adrenalin; while all the other tissues were anæmic, the coronary vessels were distended with blood, and the lungs showed a condition of the most intense congestion, being a deep plum colour. After seeing this it will take a great deal to convince me of the advisability of using adrenalin in hæmoptysis. In so far as any result will be obtained it will be a harmful one. The blood which is being squeezed out of the rest of the vessels will be forced into the pulmonary vessels, which are unable to protect themselves by adequate vaso-constriction, and hæmorrhage will be aggravated

unless the sole source of the bleeding is a bronchial vessel. I believe that the only reason why serious harm has not been done more frequently is that the drug has been administered by the mouth, so that it has had little effect; but if injected into the circulation, it would have a most injurious effect in hæmoptysis, because of the pulmonary engorgement that results.

Adrenalin in Cerebral Hæmorrhage.—For similar reasons adrenalin is contraindicated in cerebral hæmorrhage. Even admitting that there are vaso-constrictors in the vessels of the brain (and Wiggins found a slight constriction after perfusing adrenalin), the systemic rise of blood-pressure certainly outweighs any possible advantage to be reaped from a local constriction in the cerebral vessels; and local application is out of the question.

In hæmophilia, Schlesinger has given adrenalin in doses of 10 to 20 minims by the mouth for intestinal bleeding with success. Improvement has followed its use in purpura, though it is difficult to imagine how small doses of a drug which is probably not even absorbed from the stomach could affect hæmorrhages resulting from an altered condition of the blood. In the cases in which I have used it I could not satisfy myself that the improvement was more than rest and suitable diet could account for. Dudgeon has suggested, however, that purpura may stand in the same relation to acute lesions of the suprarenals as pigmentation does to chronic destruction, a view which would make adrenalin the proper treatment.

Serous Membranes.—Injection of adrenalin to prevent recurrence of ascites or pleural effusion was first advocated by Barr, of Liverpool, in 1903. A drachm of the adrenalin chloride solution in 2 drachms or $\frac{1}{2}$ ounce of sterilized water is injected through the trocar when the serous exudation has been withdrawn. In view of the transitory effect of adrenalin, it is difficult to see why this should be effective; but it apparently is. Plant and Steele suggest that as adrenalin added to serous exudation causes some coagulum, it glues together the layers, and thereby promotes adhesions. I have seen abundant fibrous coagula in the peritoneal cavity post-mortem following this treatment.

They noted pain and a rise in temperature in some of their cases as a result of the injection, but I have not seen any bad effects in the cases where I have used it with chloretone. It seems free from risk and well worth employing. But I think that the most that can be claimed for it in ascites is that it delays return of the fluid.

Surgical Applications.—Adrenalin has been very useful in certain surgical conditions, but on these I shall only touch briefly, as I have not first-hand experience of them. For removal of foreign bodies and other operations on the eye, Darier recommends 10 drops of the 1 in 1,000 solution added to 10 grammes of a 1 per cent. solution of cocaine. MacCallan thinks it is risky to employ it in glaucoma, as he has seen it cause a rise in tension. I saw an alcoholic patient

who had adopted the practice of dropping adrenalin into his eyes to diminish their bloodshot appearance, but the secondary reddening that followed the temporary constriction had left him in a worse plight than before.

Its blanching action has rendered adrenalin of considerable service both for diagnosis and treatment of diseases of the nose, for it is rapidly absorbed by the nasal mucous membrane. For similar reasons it is a palliative in hay fever.

In affections of the bladder it has been used with cocaine for anæsthetic purposes. Duncannon reports favourably on its use in catheterization, in the pain and strangury of acute gonorrhœa, and in the hæmaturia of enlarged prostate. In uterine bleeding it may be looked to to produce a double effect, constricting the bleeding vessels and causing uterine contractions. In the form of ointments it certainly seems to alleviate hæmorrhoids.

In local anæsthesia the rôle of adrenalin as an adjunct is to prevent the escape of the anæsthetic from the field of operation by constricting the blood-vessels in the neighbourhood. In this way its general toxic effect is diminished, while its local anæsthetic effect is increased. It has been proved experimentally that whereas of a subcutaneous injection of lactose one-third is excreted by the urine in the first hour, if two drops of adrenalin be added, none is excreted in that time, showing that it had not left the site of injection. In using adrenalin in this way it must be

remembered that cocaine, novocaine, and alypin either have no influence on the action of adrenalin or slightly increase it; while eucaine, tropocaine, and possibly stovaine, have a markedly antagonistic reaction, considerably decreasing the activity of the drug.

It is important that there should be no trace of soda in the fluid used for boiling the syringe employed, since adrenalin is rapidly destroyed in alkaline solutions.

B. T. Lang, in his interesting review of the subject, recommends the following three solutions of different strengths, but all, as far as possible, isotonic with blood:

	A.	B.	C.
4 per cent. novocaine with 0.1 per cent. thymol with oil of gaultheria	1 c.c.	1 c.c.	1 c.c.
4 per cent. saline with thymol and oil of gaultheria	2 c.c.	2 c.c.	2 c.c.
1 in 1,000 adrenalin with thymol and oil of gaultheria... ..	3 drops.	3 drops.	3 drops.
Distilled water up to	10 c.c.	10 c.c.	10 c.c.

It is impossible to satisfactorily anæsthetize any inflamed tissue by immediate infiltration, as the intercellular spaces are already filled with lymph, but it may be possible to attack the nerves supplying the inflamed area nearer the brain.

In spinal anæsthesia adrenalin is not so satisfactory, as it limits the spread of the injection too much. Also its use has been followed by petechial hæmor-

rhages in the brain, which may well be due to the blood being driven to a part which is unable to adequately protect itself by vaso-constriction.

Adrenalin and Addison's Disease.—Wilks' view of the 'unity of Addison's disease' now admits of restatement. It is due to the absence of adrenalin from the circulation, and this may be brought about in several ways. Our present knowledge affords a reconciliation between the two views originally held as to the pathology of this disease—one ascribing it to fibro-caseous change in the suprarenals, the other to changes in the adjacent sympathetic.

If the sympathetic cannot act in the absence of adrenalin, two of the cardinal symptoms of Addison's disease can be readily explained. As the sympathetic supplies accelerator fibres to the heart, and constrictor fibres to the bloodvessels, their paralysis must result in profound cardio-vascular atony. The sympathetic also provides the stomach with inhibitory fibres; their loss must lead to motor irritability of the stomach, and therefore to vomiting. This will be intensified because, the closure of the pyloric sphincter being under the control of the sympathetic, regurgitation into the stomach can now easily occur from the duodenum. For similar reasons, as I pointed out some years ago, it may be impossible to cause reflex dilatation of the pupil by pinching the skin of the neck.

The pigmentation is more difficult to explain. Adrenalin, like many other bodies containing the

benzene nucleus, is a chromogenic substance, and Hopkins has thrown out a suggestion that the deposit of pigment is due to 'adrenalin gone wrong,' as one might say. The chief difficulty to this tempting hypothesis is that it makes the suprarenal more of an excretory than a secretory structure; that is to say, the immediate precursors of adrenalin accumulate in the blood in the absence of a healthy suprarenal. But it is usual to regard adrenalin as being as specific a formation by the suprarenal as pepsin is of the gastric glands. Nevertheless, there is force in Hopkins' objection to attributing such indefinite powers to an animal cell when simpler chemical possibilities are available.

Adrenalin is only formed in the medulla of the gland, and until we know the function of the cortical portion we can hardly expect to comprehend all the phenomena of Addison's disease.

Occasionally the gland is found to have been completely destroyed, and yet the signs of suprarenal inadequacy have not developed. At St. Bartholomew's Hospital, during the last thirteen years, four examples of caseation of both suprarenals were discovered post-mortem which had led to no symptoms during life. Grünbaum suggests that the similar cells in connection with the sympathetic chain have assumed the function of the gland.

It must be admitted that the treatment of Addison's disease by suprarenal extract has so far been very disappointing. Nothing at all comparable to the

success of thyroid medication has been recorded. Adam collected 105 cases treated in this way, and found that in 49 it had no effect, in 39 there was considerable improvement, in 16 there was permanent benefit, while in 7 alarming or fatal results occurred. Lloyd-Jones recorded a case in which cure followed the administration of twelve tablets a day. Gullan reported two cases; in one the treatment did no good, in the other apparent recovery occurred after giving eighteen tablets a day. The best results have been in chronic cases, and ones in which there is no additional lesion elsewhere. Diminution of pigmentation has been recorded as a result of the treatment.

Among possible explanations for this lack of success may be mentioned—

1. Unlike the thyroid, which is a reservoir of the active principle, the amount of adrenalin in the gland at any moment is very small. This objection will not apply, of course, to cases where adrenalin itself is used, and not suprarenal extract.

2. It is doubtful whether adrenalin is absorbed sufficiently to be really effective when given by the mouth. We have seen that in the normal individual adrenalin causes no rise of blood-pressure when administered thus. It is true that it can produce a rise when given in Addison's disease, presumably because the vaso-constrictors of the stomach are in too atonic a state to respond. Indeed, Grünbaum has utilized this fact in the diagnosis of Addison's disease. He gives 3 grains of suprarenal extract three times a day for three days.

If a rise of more than 10 per cent. occurs in the blood-pressure, he thinks that the probability of Addison's disease approaches a certainty.

But as the tone of the bloodvessels returns, the adrenalin must defeat itself, causing a vaso-constriction which will render its own absorption increasingly difficult. This is probably the chief reason for the comparative failure of adrenalin in this disease. Repeated intravenous injections are impracticable, and would not really take the place of the steady, continued secretion of small doses into the circulation, such as the normal gland accomplishes. It is possible that in the future paragangline or the artificially synthesized substances, which are more stable, and therefore more continued in their action, may prove more successful.

Other possible reasons for failure are :

3. The gland may contain other active principles.
4. In some cases the patient is suffering from progressive tubercular lesions, which will not be checked by this treatment.
5. The cortex must have some function, and it does not form adrenalin. In this connection Bulloch and Sequeira's observations on the connection between premature sexual development and adenomata of the suprarenal should be remembered (Transactions of the Pathological Society, 1905). They suggest that the cortex may yield a hormone which influences growth of the body and the development of puberty and sexual maturity. Rolleston reminds us that if the

cortex has an antitoxic action also, as has been suggested, the administration of an extract would not replace the activities of the living cells.

Deleterious Effects.—Like all powerful drugs, adrenalin has its dangers. We need not fear these bad results from local application or subcutaneous injection, since the vaso-constriction it produces so greatly interferes with its absorption. They have only been noted after intravenous injection.

1. *Mechanical Effects of High Blood-pressure.*—The great pulmonary engorgement produced must be remembered. This seriously limits the use of the drug as a cardiac stimulant in inflammatory diseases of the lung. As the brain cannot adequately protect itself against this rise of pressure by vaso-constriction, damage may be done here also. The use of adrenalin in spinal analgesia has been followed by convulsive seizures, due to petechial hæmorrhages, which are probably produced in this way.

Repeated injection of adrenalin into rabbits has been thought to cause atheroma, aneurysmal dilations, and hypertrophy of the heart. This would accord very well with the view that anything causing a persistently high pressure will lead to arterial degeneration. But in this particular case the evidence is not as yet convincing, for other observers have found evidence of arterial degeneration even more frequently in a series of control rabbits that had not received any injections at all.

2. *Glycosuria.*—The little that is known of the

cause of this will be discussed in the chapter on glycosuria in general.

3. *Toxic Effects on the Tissues.*—Necrotic areas have been found in the centre of the lobules of the liver, outside which were areas of fatty degeneration. They have been attributed to the shutting off of the arterial blood by the intense vaso-constriction. I have seen similar changes in the liver of a child to whom I had given an intravenous injection of 15 minims, but I am not convinced that the drug was responsible, as the child had broncho-pneumonia, which often leads to fatty liver. In the kidney, cloudy swelling and desquamation of the tubular epithelium have been seen after injections of adrenalin both experimentally and clinically. However, Butler's case, in which as much as 38 minims were injected in all, recovered, so that if the damage be due to the drug it apparently is not permanent.

Summary.—Adrenalin, which is formed in the medulla, is a benzene compound probably derived from the aromatic group in the protein molecule. It is not destroyed by simple boiling, but is rapidly destroyed by oxidizing agents, which turn it brown; apparently it is quickly dealt with thus in the tissue it excites. It loses its activity in the presence of alkalies. It is probably absorbed with great difficulty from the alimentary canal. Its application to any part produces the same effect as if the sympathetic nerves to that part had been stimulated. It may be freely applied locally, though some observers think

that caution is needed in the case of the nasal mucous membrane and (in old people) the eye. Subcutaneous injections are usually safe, though repeated injections might cause necrosis in ill-nourished parts from the local anæmia it produces. Intravenous injection is the only method of producing a general, as opposed to a local, effect, and this is not free from risk. The best results have been obtained in cases of bleeding from any part of the alimentary canal, but it is also useful in vomiting, and in preventing the absorption of poisons. It is contraindicated in hæmoptysis and in cerebral hæmorrhage. It may be used to delay the return of serous exudates, and is an adjuvant to local anæsthesia. In Addison's disease it is disappointing, though improvement has followed its use in some cases.

Therapeutical applications of the other hormones on our list need be dealt with only briefly here. Those concerned with the digestive organs are discussed in other chapters; in the cases that remain the active principle has not been isolated yet, and until this is done we are working in the dark.

Ovary.—Marshall and Jolly believe that the changes in the uterus which determine menstruation are due, not to ovulation, but to an internal secretion arising from the ovary, probably from its interstitial cells. Extirpation of the ovaries in early pregnancy prevents the fixation of the ovum, and Fraenkel states that the destruction of the corpora lutea by the galvano-cautery is as efficacious as total removal of the

ovaries in bringing pregnancy to an end. Now, the corpora lutea are also derived from the interstitial cells of the ovary. It would appear that these provide a secretion which is essential to the activity of the uterine mucosa.

We have here a suggestion of the reason why the corpus luteum persists if pregnancy occurs, but soon atrophies if it does not.

It is possible that extracts of corpus luteum or of interstitial ovarian cells might be useful in those cases where abortion occurs repeatedly in the early months of pregnancy.

In animals where the ovaries have been removed, the phenomena of heat may be reinduced by the injection of ovarian extracts. This provides a reason for trying ovarian extract for the relief of symptoms following ovariectomy or at the climacteric. On the whole it has been more successful in coping with the vasomotor disturbances than with the neurasthenic symptoms. Benefit has been reported from its use in the treatment of melancholia or mania associated with uterine or ovarian disease, and in exophthalmic goitre.

Wherever the efficacy of ovarian extract is being tested, it is important that the patient should be in ignorance of the nature of the drug, in order to avoid the element of suggestion.

Mammary Gland.—Why should the mammary gland undergo hypertrophy in pregnancy and become functionally active as soon as pregnancy terminates?

No nervous connection has been made out between the uterus and these glands, so that a chemical stimulant was looked for. Starling and Miss Lane-Claypon have apparently found the source of this in the foetus. Extracts of the foetus injected into virgin rabbits led to distinct hypertrophy of the mammary glands; in multiparous but not pregnant animals the injection caused a distinct secretion of milk.

The active principle is contained in all parts of the foetus, apparently resists boiling, and can be passed through a Berkefeld filter. To the possible practical applications of these observations I need not refer here; they are entirely for the future.

In addition to the hormones on Starling's list, there are other possible examples of internal secretion that demand a brief consideration.

Placenta.—Recently interest has been excited in the discovery by Dixon and Taylor that the placenta would yield a substance that constricted the blood-vessels and increased the contractions of the pregnant uterus. This suggested that the placenta might provide a hormone which was at once a physiological stimulus to the onset of labour and a protection against post-partum hæmorrhage. It would make intelligible also the instinct possessed by most animals—including herbivora—of eating their placenta. But further research makes it probable that this substance is not present in the living placenta, only appearing as a decomposition product.

Testis.—The contrast between the condition of a person in whom the testes are undescended and one from whom they have been removed has naturally led to the opinion that these structures form an internal secretion responsible for the production of the secondary male characters, which persist in the former case.

Shattock and Seligmann found that the occlusion of the vasa deferentia does not hinder the full development of these secondary characters. We must distinguish this, however, from the effect of ligaturing the whole cord, which would bring both internal and external secretions to an end. They regard the interstitial cells as the probable source of this internal secretion, and it is noteworthy that after ligature of the vas these cells remain unaltered, although the spermatogenic tissue degenerates.

Brown-Séquard believed that subcutaneous injections of testicular extract produced a distinctly rejuvenating effect on himself at the age of seventy-two. Here the element of auto-suggestion almost certainly played a part. Perhaps because of the exaggerated claims made for it, this treatment fell into discredit, which reacted unfavourably on organo-therapy as a whole.

Poehl attempted to give a more scientific air to these observations; he prepared from the gland a crystalline substance—spermin—for which he claimed a very definite effect on metabolism. He regarded it as a catalytic agent, increasing oxidation, and thus

acting as a powerful physiological tonic. But Loewy and Richter did not find that it altered the oxygen exchange of castrated animals.

Many of the preparations of testicular substance used are rich in organic phosphorus and lecithin. When these factors, as well as those of suggestion, are excluded, the evidence as to the benefits claimed for this treatment in nervous diseases, psychoses, impotence, and a host of other conditions, shrinks to slender proportions indeed.

Thymus.—The thymus is an infantile organ that tends to disappear spontaneously, and whereas there is an association between the cortex of the suprarenal and sexual development, there appears to be an equally definite antagonism between the thymus and the sexual organs. Thus Henderson found that castration in young cattle delayed the normal atrophy of the thymus, while Paton and Goodall have shown that excision of the thymus in young guinea-pigs was followed by rapid growth of the reproductive organs. No other changes were noted beyond a diminution of the leucocytes, affecting all the varieties, which lasted for two months. We may look upon the gland as a special infantile organ for forming white corpuscles, which we know are more numerous in the circulation of the child during the normal period of activity of the thymus. As nucleated red cells have been found in the gland, it is possible that it may form erythrocytes also. No active extract has been prepared from

the organ, so there is no evidence that it forms an internal secretion.

The enlargement of the thymus in cases of Graves' disease is very interesting, in view of the development of both these glands from branchial clefts, but we have at present no idea as to the bearing of this fact on the pathology of the disease. In one fatal case I found Hassall's corpuscles (usually regarded as the remains of the epithelium of the gill-slits) enormously hypertrophied.

As Graves' disease does not occur till after the thymus should have disappeared, its persistence in this disease raises some interesting speculations. It would suggest that only those who are the subjects of persistent thymus can suffer from Graves' disease.

Since there is no evidence that the thymus forms a hormone, it is not surprising that the efficacy of thymus extracts in disease is not proven.

The association of enlargement of the thymus with sudden death is, perhaps, strictly speaking, outside our present subject; nevertheless, a brief consideration of this point may help to throw some light on the rôle of this organ. When attention was first drawn to the association, the fact was hardly realized that enlargement of the thymus was usually merely the most striking example of a general lymphatic overgrowth. The tonsils, the lymphatic glands, the Malpighian corpuscles of the spleen, and the lymphoid tissue of the intestine, are generally markedly hypertrophied as well. To this condition the name of

'lymphatism' has been given. The subject is usually an infant, though not invariably so, for cases in adolescents are not unknown. They are usually plump and flabby, with a pasty complexion. Nothing objective can be determined beyond hypertrophy of the tonsils, and perhaps a slight swelling of the thyroid; sometimes dulness over the sternum may be detected.

Death may be quite sudden, as seen by the following description: 'While I was standing at the side of the cot the child suddenly sat up, its eyes became fixed, it ceased to breathe, became very slightly blue and then quite white, and fell back dead. The whole series of events occupied less than thirty seconds' (Thursfield). But death is not always so dramatically sudden as in this case. Sidney Phillips has recorded a case in which a child of five suffered severely from thymic asthma for three days, and then succumbed to heart failure.

The subjects of lymphatism succumb readily to anæsthetics; chloroform and ether seem equally dangerous. The usual history is that after a brief administration of the anæsthetic the patient goes rigid, or has a slight tetanic convulsion, and dies forthwith. It is possible that some of the cases of sudden death while bathing are due to lymphatism.

Three explanations have been given of sudden death in this condition:

1. *Pressure* on the trachea, the vagus, or its branches. Improbable as it may seem that a soft organ like the thymus could occlude a firm ring like the trachea, it

must be admitted that flattening of the trachea has been observed post-mortem, and relief of dyspnoea has followed raising of the gland from the trachea by operation. Thymic death is not from asphyxia, however, but from syncope.

Similar objections may be urged against the hypothesis of pressure on the recurrent laryngeal nerves producing laryngeal spasm. Such spasm to be fatal must be bilateral, and the right recurrent laryngeal nerve hardly enters the thorax at all. Moreover, there is not the typical crowing inspiration of laryngeal obstruction.

Pressure on the vagus is possible, and would cause syncope.

2. *Intravascular clotting* from hyperthymia. It is true that an extract of thymus gland will cause intravascular clotting, and therefore sudden death, but such an extract cannot be held to represent a normal internal secretion of the thymus. Similar extracts can be prepared from lymphatic glands or the testis, and simply owe their activity to the thrombokinase they contain. Moreover, intravascular clotting is conspicuously absent in cases of 'thymic death.'

3. *Toxæmia*. The general hypertrophy of the lymphoid tissue suggests that the body is reacting to some infective process. The great tendency of adenoid tissue in children to react to irritation is well known. On this view the death is merely the terminal event of a prolonged intoxication, the nature of which is at present quite unknown. Sidney Phillips thought that

the symptoms in his case strongly suggested a toxic agency.

Pituitary Body.—In its double origin, in part nervous, in part epithelial, this structure offers an interesting parallel to the suprarenal capsule. In both it is the part of nervous origin that contains the active principle, and in both the nervous elements disappear during development. The pituitary body has long been a fascinating puzzle to the morphologist, and since its association with acromegaly has been known, it has offered many problems to the pathologist also.

In studying the functions of a ductless gland, three main methods of inquiry are open to us: we can note the symptoms produced by disease of the organ, the effect of extirpating it, and the physiological action of extracts prepared from it. Now, in the case of the pituitary body, these lines of research have led to contradictory results.

Experimental removal of the gland has been followed by anorexia, lassitude, diminution of the body temperature, dyspnœa, and muscular twitchings, going on to spasms. Some of these symptoms probably result simply from the severity of the operation, and none of them are characteristic features of acromegaly. Herring has shown that the most marked effect of pituitary extract is on the circulatory system, being on the one hand accelerator and augmentor to the heart muscle, and on the other

stimulating its inhibitory nervous mechanism, while it constricts the bloodvessels. The pituitary body is said to contain iodothyronin, and to enlarge after excision of either the thyroid or suprarenal.

There is no real agreement as to whether the symptoms of acromegaly are due to overaction or underaction of the pituitary body, and so far extracts of the gland have not succeeded in alleviating the disease. The glycosuria, which sometimes accompanies it, is possibly due to pressure on the fourth ventricle, and has been observed in cases of pineal cysts also.

Kidney.—There is no evidence of the existence of an internal secretion formed by the kidney. Rose Bradford observed increased excretion of urea after removal of a considerable proportion of the substance of the kidneys in dogs, and this has been thought by some to point to a regulation of nitrogenous metabolism by an internal secretion. Beddard and Bainbridge have shown, however, that a more probable explanation is that this rise in nitrogenous output was simply that seen in the later stages of starvation from any cause. Extracts of kidney have not met with any therapeutical success.

Muscle.—The use of meat-juice (zomo-therapy) in pulmonary tuberculosis, and of meat-extracts to stimulate secretion of acid in the gastric juice, may also be classed as examples of organo-therapy.

Though many other organic extracts have been employed, it cannot be said that they have achieved,

or, for that matter, have deserved, success; for the preliminary proof that the extracts contained any active principle whatever has been lacking. Starling looks forward to an important future for organo-therapy conducted on right lines when he says: 'If the mutual control . . . of the body be largely determined by the production of definite chemical substances in the blood, the discovery of the nature of these substances will enable us to interpose at any desired phase in these functions, and so to acquire an absolute control over the working of the human body. Such a control is the goal of medical science.'

Far though we may be from such a goal, the study of hormones offers a profitable field for pharmacological research. For it is only by an exact knowledge of the bodily processes in health that we can learn to intervene effectively in disease.

CHAPTER II

THE RATIONAL TREATMENT OF GASTRIC
DISORDERS

DURING the past few years such important additions have been made to our knowledge of the digestive processes that it may be well briefly to consider the bearing of the new facts on the rational treatment of gastric disorders.

The Nervous Factor in Gastric Digestion.—It is to the Russian school of physiologists that we owe the most fundamental experiments on this subject. Pawlow, by dividing the œsophagus in dogs, and fixing both of the divided ends to the skin, completely separated the cavities of the mouth and stomach. Food taken into the mouth would naturally drop out of the gullet; this is termed ‘sham feeding,’ but ‘direct feeding’ could also be carried out by passing food in the stomach by way of the lower segment of the œsophagus. In some cases a separate cul-de-sac was made out of a portion of the stomach. This pocket opened on to the surface, so that the digestive processes in it could be easily observed; it

was found that they were an exact reflection of those occurring in the main stomach.

He found that in such a dog the taking of food by the mouth was followed after an interval of five minutes by a copious secretion of gastric juice; in fact, it was not necessary for the food even to be swallowed. If the dog were shown the food, secretion would follow, until the animal realized it was not going to get it.

Clearly, a nervous agency must be at work. Now, if one vagus were previously divided below the recurrent laryngeal and cardiac branches, and the other drawn into the wound, the latter could easily be cut while the animal was feeding. It was found that now 'sham feeding' produced no effect. Conversely, if the vagus had been previously drawn into the wound and divided, to allow the cardio-inhibitory fibres to degenerate, it was found that stimulation of the peripheral end, too weak to cause the animal any pain, led to a secretion of gastric juice.

On the other hand, 'direct feeding' into the stomach led to hardly any secretion, if the animal did not see the food.

The value of an appetite in aiding digestion was more clearly proved by the following experiment: Two dogs had 100 grammes of meat introduced direct into the stomach; one dog's attention was distracted, so that he did not know he had received food, while with the other a vigorous 'sham feeding' was kept up at the same time. In equal times the first dog digested only 6 grammes, while the other digested 30.

The difference represents the digestive value of the passage of food through the mouth, and the consequent rousing of the appetite.

The character of the juice poured out varied greatly with the diet that excited it. Thus, a meal of bread caused the secretion of a small amount of juice, rich in pepsin, but poor in acid. Meat caused a much larger secretion of a juice weaker in peptic power, but containing more acid. Milk required even less pepsin than meat to digest it.

The Chemical Factor in Gastric Digestion.—Mechanical stimulation of the gastric mucosa will lead merely to an outpouring of alkaline mucus, but certain chemical stimuli will result in true secretion. As clinically chemical factors are much more under our control than nervous ones, these results are important.

We may arrange the effect of articles of diet as follows :

1. Substances producing a powerful secretion: Meat extractives such as are continued in soups, broths, and beef-tea. The secretion begins in thirteen minutes. Bickel found that in human beings the following substances also produced an abundant secretion: alcoholic and carbonated fluids, spices, mustard, pepper, salt, cloves.

2. Substances producing a slight secretion: Milk, gelatine, water.

3. Substances producing no secretion: Egg-white, proteose, peptone, starch, sugar, salts of meat.

4. Substances inhibiting secretion : Fats and sodium bicarbonate.

In fact, the secretion occurs in two stages, the first depending on the stimulation of the sense of taste while the food is yet in the mouth, the second occurring when absorption has begun. The mechanism of this second secretion has been shown by Edkins to depend on a chemical factor, which would explain the occurrence of digestion after division of the vagi. The pyloric glands differ widely in structure from the glands in the fundus of the stomach. Though the latter are simple tubular glands, they are composed of highly differentiated cells, the granular chief cells secreting the pepsin and rennin, the ovoid parietal cells forming the hydrochloric acid. Passing to the pylorus, we find a marked change in the plan of the glands, which have become wide-mouthed and branched; the lining cells are neither granular nor ovoid, but closely resemble those lining the surface of the stomach.

No theory of gastric secretion can be altogether satisfactory that does not account for these striking differences of structure. It is the merit of Edkins' work that it at once explains the structural difference and the method of secretion in the absence of nervous impulses.

He found that an extract of pyloric mucous membrane injected into the circulation of a fasting animal would cause the secretion of a juice containing both hydrochloric acid and pepsin. A similar extract of

fundus glands produced no effect. Pyloric glands, therefore, produce a chemical stimulant or hormone to the continued secretion of gastric juice by the fundus glands. This is termed *gastric secretin*.

He then divided the stomach into two portions by a tampon, and was able to prove that all the active juice was formed in the fundus, while the function of the pyloric portion was absorptive.

And, indeed, if the appetite and sense of taste were the only stimulants to secretion, how would digestion be completed when the former was assuaged and the latter no longer exercised? Many animals, their hunger being satisfied, soon fall asleep. We can see now that the secretion, started by nervous impulses, is continued by chemical stimuli, which will act as long as there is food in the stomach. This accords very well with what has been observed on the X-ray screen, both in men and animals to whom bismuth has been given with the food. Long after the fundus has returned to its fasting appearance, the pyloric portion contains food, and shows those vigorous waves of contraction which form the 'gastric mill.' The semi-digested food is thus kept in close contact with the glands in which the stimulant to gastric secretion is elaborated, and thus provides for its own digestion.

It has been noticed by Hertz that the later stages of a meal may be retained at the cardiac end, while the earlier stages are being vigorously churned at the pyloric part. The stomach now shows two separate shadows on the screen, which might lead to the

diagnosis of an hourglass contraction. This is, however, a normal occurrence, which enables salivary digestion to continue at one end, while gastric digestion is proceeding at the other. It is probably related to the fact that we find the glands at the cardiac end, like the pyloric, are simply mucous in character, peptic glands being limited to the fundus. For confirmation of this, I might point to the fact that these cardiac glands are specially extensive in an animal like the pig, which eats largely of carbohydrates.

Practical Deductions.

The nervous factor in gastric digestion affords a scientific explanation of the old adage, 'Hunger is the best sauce.' Indeed, as we have seen, it is a sauce which will increase the rate of digestion fivefold. This must lead us to attach the highest importance to the personal equation in dieting a patient. Too rigid a dietary, albeit compiled on an admirable chemical basis, may prove distasteful and upset the appetite, thereby preventing all the good it might be expected to effect. Nevertheless, in neurotic patients the very rigidity may cause interest, and thus excite the appetite. A remarkable example of this I once saw in a typical neurasthenic. He complained that his food 'did him no good,' and he lost flesh until, becoming alarmed, he underwent a 'cure' in Germany. It depended on an exact analysis of all the excreta, on the result of which the menu for the

next day was drawn up. This process, which would have been repulsive to the average man, excited his interest keenly, and he thrived greatly. He is now firmly convinced of the unscientific character of English physicians. The personal equation is, I think, too often neglected. Thus, fat has an inhibitory effect on gastric secretion in any case; to force it on a child who loathes it may be good moral discipline, but it is certainly bad physiology.

Our dietetic restrictions and prescriptions are too much dictated by fashion. Except in cases where we must forbid something for a perfectly definite reason, our patient's likes and dislikes should be carefully considered; instead of which it is our own likes and dislikes which reappear constantly in our dietetic schemes. Given a certain knowledge of the man, one can predict fairly accurately what he will recommend to any patient. The dyspeptic is often a diligent seeker after medical advice, and when he tries to harmonize the various dietetic gospels he has received, his opinion of our profession is not enhanced.

'There is to be observed a sort of fashion running through these restrictions,' says Sir William Roberts, 'yet I know not on whose authority they repose. I do not think it is any medical authority. My impression is that most of them derive their origin from some crude notions floating through the lay press, and unconsciously lodged in the medical mind. . . . They are, for the most part, quite unmeaning; they stand on no ground of science or

experience, and are gratuitously punitive to our patients. . . .

‘There are cases in which a certain amount of coercion is salutary and even necessary. In neurotic and hysterical persons the stomach sometimes shares in the general instability, or it may even be the chief offender. I have known such stomachs reduce their hosts by successive acts of self-inflicted restrictions to a diet of dry toast and water gruel.’

Yet it is extraordinary that in many cases quite opposite methods of restriction should both be successful. A patient goes to one physician, whose opinion is that all purins are deadly poisons. He is put on a purin-free diet, and improves. Tiring of the restrictions, he seeks other advice. He comes across another physician, whose opinion is that most ills are due to incomplete combustion of carbonaceous foods. These are now restricted, while he takes meat freely, and again he improves.

Of course, the explanation is that this is a type of patient who eats and drinks too much. Variety of diet stimulates his appetite, while the monotony entailed by abstention from so many pleasant things results in his eating less altogether.

In fact, there are really surprisingly few instances in which the addition of or abstention from some particular article of diet can be relied upon to produce a specific effect. Examples will be considered in their appropriate places.

The late Sir Andrew Clark was accustomed to

forbid his dyspeptic patients to take soup, on the grounds that, by diluting the gastric juice, it prevented digestion from proceeding. The advice was good in many cases, though the explanation was unphysiological. At this stage the gastric juice has not been secreted, and therefore it cannot be diluted. Moreover, of all the chemical excitants of gastric secretion, meat-extracts have proved the most efficacious. To a tired man the warm fluid, causing gastric vaso-dilatation, and containing a stimulant of the gastric juice, while not in itself taxing the digestive organs, is an excellent beginning to a meal. It is important to note that, although meat-extractives increase the quantity of gastric juice, they involve little secretion of pepsin, and mainly affect the production of hydrochloric acid. In hyperchlorhydria, therefore, meat-soups are distinctly contraindicated, while in dyspeptics with inadequate gastric secretion they are beneficial.

We can now explain the discrepancy between the results of analysis of meat-extracts and the popular estimate of their value. Their nutritional worth, so far from being accurately represented by pictorial advertisements, is stated to be equivalent to that of a teaspoonful of milk in a tumblerful of water. Yet as stimulants of gastric juice they have a decided place, and a patient may be able by their aid to tolerate a restricted and uninteresting dietary. But we must remember that we are not giving food; we are only preparing the way for food.

The tax which vegetable protein imposes upon the pepsin as compared with animal protein should not be forgotten in the construction of a dietary. The energy thus used up in gland metabolism must be deducted from that of the ingested food. Herein lies the advantage of lightly cooked minced meat ; it requires little pepsin, it does not easily ferment, and it does not leave a large indigestible residue. It is for this reason that it has proved useful in dilatation of the stomach and in ulceration of the large intestine. Surely it is a fallacy to administer so much starchy food in dyspepsia as is frequently done, when we consider its liability to ferment and the quantity of juice required for its digestion. A preparation that looks like milk does not necessarily become digested like milk ! Harry Campbell has protested strongly against starchy foods in the form of pap. It has to be swallowed at once, without any chance of salivary digestion, while in the solid form, requiring a good deal of mastication, it excites enough secretion of saliva to initiate its conversion into sugar. It is for this reason that toast and biscuit can often be digested when new bread or mashed potatoes cannot.

In many respects the physiologist's discoveries have been anticipated by the chef. We see the advantage of beginning a meal with soup to excite secretion, and of finishing with sweets, when the cardiac portion of the stomach will retain the food and permit continued digestion of the carbohydrates by the saliva. We can realize, too, that the surround-

ings of a meal may have a physiological as well as an æsthetic value.

Pawlow's experiments may also explain the different value attached to bitters by the clinician and the pharmacologist. It is true that, introduced directly into the stomach or into the circulation, bitters are ineffective, but by exciting the nerves of taste and arousing the appetite while passing through the mouth they may still be a decided aid.

An important application of this point is the treatment of patients on whom gastrostomy has been performed for stricture of the œsophagus. That the stricture is usually malignant is held to be sufficient explanation of the fact that such patients do not thrive. But we see now that they are losing the powerful aid of 'appetite juice,' since the food no longer passes through the mouth. It is only rational, then, and it is very easy, to accompany feeding through the gastrostomy wound by the taking of sapid substances into the mouth which will excite the sense of taste.

I knew of one case in which the patient himself requested that he might take the food into his mouth and, after mastication, place it in his stomach through the gastrostomy wound. The request was granted, and the change seemed to benefit him. It was considered merely an unpleasant eccentricity on his part, whereas really he had anticipated Pawlow's discovery.

The Acid of the Gastric Juice.

Of all the constituents of the gastric juice, the hydrochloric acid is the most variable. Pepsin disappears in atrophic gastritis, and is much diminished in gastric carcinoma, but otherwise alters very little in disease. How important the hydrochloric acid is throughout we can see on enumerating its functions.

1. It is essential to the activity of the pepsin, which is powerless in a neutral medium.

2. It is antiseptic.

3. It hydrolyzes starch to some extent, like any other mineral acid.

4. The presence of hydrochloric acid in the duodenum regulates the pyloric sphincter.

5. It is a stimulant to the pancreatic secretion.

In gastric disorders, without structural change, it is the hydrochloric acid that holds the key to the situation.

If there were no hydrochloric acid, there would be no digestion in the stomach, while fermentation would proceed apace in the absence of the normal antiseptic; whereas, if there were excess of acid, the following results might be expected:

1. Pain, especially towards the end of digestion, when the stomach is getting empty. The pain, therefore, comes on sooner after a light meal, such as afternoon tea, than after a heavy meal. Thus, after evening dinner there may be freedom from pain till the middle of the night.

2. **Pyloric Spasm**, excited by each gush of highly acid chyme into the duodenum ; and thus, though gastric digestion would be proceeding, the onward progress of the food would be delayed.

3. **Pyrosis**.—This term should be kept, as Sir William Roberts advised, to a paroxysm of gastric cramp, accompanied by a sudden gush of saliva into the mouth. It is an attempt on the part of the body to neutralize the excessive acidity of the gastric juice by the alkaline saliva, but, like so many pathological attempts at repair, it overshoots the mark ; for it is impossible for such a quantity of saliva to be swallowed.

4. **Appetite for Indigestible Things**.—The patient feels more comfortable when the gastric juice is given plenty to do, and therefore he often eats largely. There may be a positive craving for fat, which is comprehensible when we recall its inhibitory effect on gastric secretion.

The principal conditions under which the acid of the gastric juice is deficient or absent are—

1. **Chronic gastritis**.

(a) Simple atonic, in which only the hydrochloric acid is reduced.

(b) Mucous, in which the acid is reduced, while the mucus is considerably increased.

(c) Atrophic, in which hydrochloric acid, pepsin, and rennin are all alike absent.

2. **Malignant disease**.

The absence of hydrochloric acid from the gastric juice in malignant disease of the stomach is usual,

but not invariable. Thus, in a series of eight cases, French found it absent in five, but present in three. Various explanations have been given for its disappearance.

(i.) Reissner found that, although there was loss of free hydrochloric acid in the gastric juice, the total chlorides were not decreased. This would point to a neutralization by alkalies, which have been found in the fluid secreted by the surface of a new growth. This could only occur when there had been loss of the superficial epithelium.

(ii.) B. Moore and his colleagues maintain that there is a low secretion of free hydrochloric acid when malignant disease is present anywhere in the body, and not simply in the stomach, due to a diminution of hydrogen ions in the blood. While it seems clear that if metabolism be sufficiently depressed the output of acid is decidedly affected, it is perhaps too much to claim that malignant disease is peculiar in this respect. While hydrochloric acid may be absent in any cachectic condition, the active acid is not necessarily diminished in early or uncomplicated carcinoma of organs other than the stomach. And, as Willcox points out, it is absurd to draw a distinction between free HCl and HCl combined with protein.

(iii.) Another factor that seems to me to have been overlooked is the loss of the gastric secretin, which is a powerful stimulant to the secretion of the acid. The pyloric region is the one most frequently affected by cancer, and though hydrochloric acid is not formed

there, destruction of the pyloric glands involves the loss of the chemical factor in gastric secretion.

With all these influences—neutralization, depressed metabolism, and loss of the chemical stimulant—at work, the absence of free hydrochloric acid is not surprising.

The principal conditions under which the acid of the gastric juice is increased are—

1. 'Sthenic' dyspepsia, or the so-called acid dyspepsia of healthy persons.

2. Peptic ulcer, gastric or duodenal.

The contrast between the atonic or asthenic dyspeptic, in whom the hydrochloric acid is diminished, and the sthenic type, in which it is increased, has been vigorously drawn by Leonard Williams ('Minor Maladies,' p. 43).

'The sthenic form occurs in people who seem otherwise to be in robust health—people who are for the most part strong, active, and energetic, and who are seldom teetotallers. The asthenic form appears in weakly, nervous, convalescent, or overworked persons who may be teetotallers, but who are generally tea-drinkers. The one is essentially an active, positive, the other a passive, negative, type; and the distinctions between the symptoms are in consonance with these characteristics. The sthenic tongue is firm, and generally furred; the asthenic is flabby, frequently indented at the edges, and generally clean and glazed. The sthenic pulse is slow and full, the asthenic quick and feeble. The sthenic appetite is

voracious and ever present; the asthenic is weak, capricious, and often absent. In the sthenic the discomfort consists in a sense of epigastric fulness; in the asthenic it consists of actual pain in the epigastrium, striking through and between the scapulæ. In the sthenic a full meal relieves the symptoms; in the asthenic it aggravates them. In the sthenic the mental state is one of irritability; in the asthenic it is one of depression. But perhaps the most striking, as it is certainly one of the most diagnostic, distinction is presented by the period of onset of the symptoms. This, in the sthenic, is delayed until towards the end of the digestive process—that is, from four to five hours after a full meal—whereas, in the asthenic, the discomfort, always more or less present, becomes acute within half an hour of the ingestion of food.'

On this striking description I have but two criticisms to offer: the tongue has certainly not been clean in cases of asthenic dyspepsia which I have seen, where the diminution of hydrochloric acid has been proved by a test-meal. And as far as I can judge from the descriptions given me by sufferers from sthenic dyspepsia—some of them medical men—to call the pain merely 'a sense of epigastric fulness' is to understate its severity. Moreover, as he himself says—and I can quite confirm it—'the manifestations of sthenic dyspepsia are liable very closely to simulate angina pectoris.' Now, the pain of angina pectoris is much more than a sense of fulness.

It would appear that this type of dyspepsia is

usually due to over-activity of the secretory nerves rather than to structural change in the glands. Thus we can understand why it occurs in the type of man it does, and why that man 'who in the prime of manhood was a martyr to dyspepsia . . . in his later years, when his nerves are blunted . . . eats and drinks with the courage and success of a boy' (Foster).

Another factor in the production of hyperchlorhydria which I have noted in several cases is a sudden change of diet, such as occurs during a Continental holiday.

Principles of Treatment in Asthenic Dyspepsia (Achlorhydria).

It goes without saying that in all forms of gastric affections the condition of the teeth calls for attention. Carious teeth mean that mastication cannot be duly performed, and that septic absorption is taking place.

Several years ago Bunge directed some pertinent criticisms against the indiscriminate use of alkalies in fermentative dyspepsia. While it is quite true that an alkali, by neutralizing the acids of fermentation, will relieve the symptoms, it will also neutralize the hydrochloric acid of the gastric juice, without which pepsin is powerless. As this acid is also antiseptic, fermentation will proceed apace in its absence, while digestion is arrested.

Except as a palliative, the usefulness of alkalies in conditions associated with diminished hydrochloric acid is limited to their administration before meals.

Even then it is not obvious how alkalies act beneficially, though the fact is undoubted. It used to be stated that they stimulated the flow of gastric juice, though it was not clearly proved that they provoked more flow than was necessary to neutralize them. Pawlow, however, finds that they inhibit the flow of both gastric and pancreatic juices. He believes that they insure physiological rest to a stomach which is in a condition of irritable weakness, and compares their action with that of digitalis in restoring compensation to the heart by prolonging diastole.

Whether this explanation be correct or not, the solvent action of alkalies on mucin must surely be a help to a stomach hampered by catarrhal exudation, enabling digestion to start with a clean slate, and, still more important, allowing of the absorption at the pyloric end, which is necessary for continued gastric secretion.

While too much reliance has perhaps been placed on alkalies, certainly the use of acids had been somewhat neglected.

We know that not only is the hydrochloric acid essential to the activity of pepsin and to the secretion of pancreatic juice, but that it is a valuable antiseptic, and helps the hydrolysis of the fermentable carbohydrates. We know also that its secretion fails in gastritis long before the pepsin disappears. Yet we still see dyspeptics sprinkling pepsin powders over their food while spurning the aid of hydrochloric acid. Again, in asthenic conditions of the stomach,

the flow of juice starts briskly enough, and may even be greater than normal in the first hour (Sawriew), but it is not maintained. Here, too, the use of hydrochloric acid after meals is a rational and even a necessary procedure. And we should not be niggardly; for even the full pharmacopœial dose of 20 minims would only confer an acidity of 0.02 per cent. on a pint of fluid.

The combined use of alkalis before meals, followed after meals by a good dose of dilute hydrochloric or nitro-hydrochloric acid with *nux vomica*, has given me more satisfactory results than either separately. Acidol (betain chloride) has the advantage of gradually giving off hydrochloric acid in aqueous solutions, and should be employed wherever the simple acid disagrees for any reason. It is quite stable in the dry state, and is readily soluble in water. Pastilles containing $7\frac{1}{2}$ and 15 grains are put up, and are equivalent to about 5 and 8 minims of hydrochloric acid respectively. They should be given freshly dissolved, and not swallowed in the solid form. Patients usually tolerate the acid in this form without difficulty.

But cannot we induce the glands to form the acid for themselves? Remembering that interaction between phosphates and chlorides is the probable source of the acid, it might be thought that by increasing the phosphates of the blood more chloride would be set free as hydrochloric acid. But I have not had any success with this plan—very possibly

because the phosphate is rapidly excreted by the kidney; at any rate, the acidity of the gastric juice did not rise. The use of meat-extracts of various kinds has given me better results, and I believe they have an important clinical value as excitants of the secretion of acids.

In order to obtain appetite juice the idiosyncrasies of the patient must be studied, and I have often allowed some food for which the patient had a special liking, even though it may have a bad reputation in dyspepsia. And the result seems to have justified this course. Articles which obviously disagree will naturally be prohibited, and it will usually be found that fats or meat with much fat in the fibre cannot be tolerated, because of their inhibitory effect on gastric secretion. As already explained, carbohydrates in the form of pap should be avoided.

Both in this and in the opposite condition of hyperchlorhydria it will, of course, be necessary to see that the bowels are freely opened. Small divided doses of calomel, followed by a saline purge, form an important preliminary to the treatment.

Principles of Treatment in Sthenic Dyspepsia (Hyperchlorhydria).

Here the administration of alkalies after meals is a rational procedure, and 15 to 20 grains of bismuth oxycarbonate should be given about an hour after meals. Sodium bicarbonate may be combined with it, but it is the experience of many that this drug by

itself affords but a temporary relief. Walter Broadbent has found magnesia a useful addition to the bismuth mixture. Few things are more effective than the bismuth lozenges of the British Pharmacopœia as recommended by Sir W. Roberts. These should be sucked slowly, thus providing for the swallowing of much alkaline saliva as well as the alkaline drugs. Their portability is another factor in their usefulness to sufferers, who are often of an active temperament. It might be expected that belladonna would have a good effect because it is a powerful suppressor of secretion, but personally I have found it disappointing.

Kaufmann believes a lack of gastric mucus is a factor in the production of the pain. He advises lavage with silver nitrate solution, 1 in 5,000 up to 1 in 1,000, which will cause secretion of mucus and relieve pain. Pills of the same drug have been found useful for the same reason. The treatment should not be continued more than a week or ten days, to avoid the risk of argyrisms.

A teaspoonful of olive oil often relieves the pain; its action is partly mechanical and partly chemical, coating the irritable surface and inhibiting the production of acid.

As to diet, the principles laid down by Walter Broadbent (*Lancet*, 1904, vol. i., p. 867) are rational, and can be warmly recommended.

It is based on the following experiments of Pawlow:

1. The more rapidly gastric juice is secreted, the greater its acidity.

2. Flesh produces more gastric juice, and that more rapidly than bread; bread produces more gastric juice, and that more rapidly than an equivalent protein value of milk.

3. Milk produces no 'appetite juice.'

4. Cream and fat delay the secretion of gastric juice.

Therefore the diet that should be ordered at first is cream and milk only; then bread and milk, and soft milk-puddings, such as cornflour; later, bread and butter and buttered eggs, which can be earlier tolerated than any other form of egg, perhaps because the butter protects the egg until it gets into the duodenum; then fish, and finally meat. Soup and beef-tea must be entirely excluded, since they promote secretion of gastric juice without containing the protein necessary to fix the acid. I now employ this diet in all such cases, and have found it give very satisfactory results.

Physiological Principles in the Treatment of Gastric Ulcer and its Sequels.

Without going into the vexed question of the pathology of gastric ulcer, it should be noted that Hale White has urged that hæmatemesis in young women is by no means always due to ulceration, but more often to a general oozing from the mucous

membrane, for which he suggests the name of gastrostaxis. It has happened that some of these cases have been operated on for the hæmorrhage, and that no sign of ulceration could be found.

During a period of eight years 428 cases were admitted to the medical wards of St. Bartholomew's Hospital as gastric ulcer. Grouping them according to sex and mortality, it appears that there were 366 females, of whom 20 died (5·3 per cent.), and 62 males, of whom 22 died (36 per cent.).

Now, it is very striking to find that the actual mortality was almost exactly equal in the two sexes, while a very large proportion of the successful female cases occurred under thirty. It certainly suggests that in young females we have another cause for hæmatemesis. On going into the histories of the female cases I have seen since Hale White's paper appeared, it seems to me that they fall into two categories:

1. Those in which there is a very slight history of gastric pain preceding the hæmatemesis. These are usually very amenable to treatment, and are probably cases of gastrostaxis.

2. Those with a definite history of gastric pain. They are less amenable to treatment and more liable to relapse; they are probably cases of true ulceration.

When the existence of gastrostaxis is clearly established, we shall have, in all probability, to modify our conceptions as to the success of medical

treatment in gastric ulcer, and shall have to recognize that the percentage of cases in which relapse occurs is very high.

The orthodox treatment for hæmatemesis is, of course, to secure physiological rest for the stomach. After an initial injection of morphia, and a dose of 30 minims of adrenalin chloride solution in $\frac{1}{2}$ ounce of water by the mouth, rectal feeding is started about twelve hours after the hæmorrhage.

Recently, however, the value of nutrient enemata has been seriously questioned. We may admit at once that the power of the large bowel to digest food-stuffs is very slight. Whether undigested albumen can be digested at all is only of theoretical interest; it is certainly absorbed in much too small an amount to make it of any value if thus administered. The only proteolytic ferment secreted by the intestine is erepsin. This ferment, described by Cohnheim in 1903 in the succus entericus, has also been shown by Vernon to be present in all tissues in proportion to their chemical activity, and is probably an important agent in intracellular digestion. Its action is to complete the disintegration of proteins beyond the stage of peptones into simpler bodies, in which form they are absorbed. It can also act on caseinogen and fibrin.

That milk has been found the most satisfactory basis for nutrient enemata may be due to the fact that erepsin can digest some of its protein. As erepsin ordinarily acts after pancreatic juice, however, we

should naturally predigest the proteins by liquor pancreaticus before administering them *per rectum*; this has a further advantage over merely peptonizing agents in digesting carbohydrates and fats also. Ten per cent. is believed to be the best concentration for proteins in rectal feeding. As cow's milk contains 4 per cent. of proteins, it would be necessary to add 2 drachms of protein to a 4-ounce enema to bring it up to a proper strength. A milk protein, such as protene or plasmon, is a convenient method of doing this.

Normally, carbohydrates are absorbed by the bowel as dextrose, and of all the food-stuffs, this appears to be best utilized in rectal alimentation. Again, 10 per cent. is thought to be the best strength. I have found, however, that in this concentration it is apt to cause some pain, probably because of the osmotic currents it must produce. At any rate, when added to cow's milk, which itself contains 4 per cent. of lactose, 5 per cent. of added dextrose is as much as is well borne. This means that about 2 drachms of dextrose can be added to a 4-ounce enema. Even in this strength it may cause pain.

Fats are probably absorbed very indifferently under these conditions. No emulsion, however fine, is appreciably absorbed in the absence of a fat-splitting ferment. This ferment is normally supplied by the pancreatic juice, and in its absence we should have to depend upon bacterial decomposition. It is a simple matter to provide the ferment by liquor

pancreaticus, but even then absorption may be very imperfect. In one of Edsall's and Miller's cases only 13·61 per cent. of the fat was absorbed. The fat in the yolk of egg is considered to be better absorbed than other forms of fat, but personally I do not employ eggs in rectal feeding, for they add to the nursing difficulties, already sufficiently great. Should any of the egg be returned, it is very offensive.

The nutrient enema which I have found best on the whole is—

4 ounces of milk.
 2 drachms of plasmon.
 2 drachms of dextrose.
 20 grains of bicarbonate of soda.
 1 drachm of liquor pancreaticus.
 5 minims of tinct. opii.

The liquor pancreaticus is allowed to act for twenty minutes at 37° C., the opium being added just before administration, its purpose being to increase the tolerance of the bowel. The bicarbonate of soda is added to imitate the normal alkalinity of the pancreatic juice (1 per cent.). This enema is given every four hours, the rectum being washed out also night and morning. The total food-stuffs thus given in the twenty-four hours amount to—

Proteins	75 grammes.
Carbohydrate	75 „
Fat	27 „

This is clearly much less than the minimum required to keep the body in nitrogenous equilibrium,

even supposing it were all absorbed, which is very far from being the case.

- . The larger enema—1 pint of milk three times a day—has not yielded me very good results, however, the patients usually failing to retain them after the first day or two. I have no personal experience of the enema administered continuously, drop by drop, but I have heard from those that have that it caused the patients so much discomfort that they were forced to abandon them.

The normal absorption of digested food is a function not of the large, but of the small intestine. For this the villi are chiefly responsible, and as these are lacking in the large intestine, we must expect its absorptive power to be imperfect. Yet Sharkey found that 75 per cent. of the solids were absorbed in some of his cases, in which he used sugar, peptones and pulverized casein, these being, in his opinion, the best materials for rectal alimentation.

Though it can hardly be possible for a nutrient enema to reach the small intestine, it is probably diffused over a large area of the colon by virtue of the reversed muscular waves that occur in the proximal portion of the large bowel. So that, though the absorptive capacity per unit of surface is small, the total amount absorbed may thereby reach the remarkably high figures found by Sharkey. A possible fallacy in his results is that they are based on estimation of the nitrogen in the washings from the bowel. That nitrogen cannot be recovered from the

bowel does not prove that it has been utilized by the tissues, and I prefer estimating the nitrogenous output in the urine as a more accurate criterion.

That at best, however, rectal feeding means partial starvation is admitted ; there is usually a progressive loss of weight, and symptoms of acid intoxication may occur. Laidlaw and Ryffel estimated the nitrogenous output in a case of rectal feeding during coma, and found that it was approximately equal to that obtained in the later stages of fasting—as, for instance, with the professional faster Succi from the fifteenth to the twentieth day. The nutrient enemata in this case contained the white of nine eggs, 6 ounces of raw starch, and 24 ounces of peptonized milk in the day. It may be remarked that egg-white would not be readily absorbed, while it is doubtful if starch can be digested by the large intestine at all.

The element of suggestion must not be forgotten in rectal feeding. Even though the amount of absorption may not be large, patients are more contented because they think they are being fed.

As disadvantages must be mentioned—(1) the difficulty in keeping the patient in a cleanly condition, and (2) the secretion of gastric juice which it causes. It is hardly securing a condition of physiological rest to allow the juice to be poured over an ulcerated surface without having any food on which to act, especially as the excessive acidity of the juice is very likely a factor in producing the ulceration. To neutralize this juice I am accustomed to give the

patient bismuth lozenges to suck. This serves both to neutralize the juice and to form a protective covering to the ulcer. At the same time, by keeping the salivary glands active, it diminishes the chances of an ascending parotitis. I am quite sure that this makes it much easier to keep the mouth clean. Incidentally, I should like to protest against the use of glycerin in a mouth-wash in this, or, indeed, in any other condition. The desiccation which follows only aggravates the state of the mouth. Plain, hot water, to which a little potassium permanganate has been added, is, in my opinion, much to be preferred. Ice is also objectionable; though pleasant at the time, it aggravates thirst.

It is well known that the body can stand deprivation of food if water be supplied. W. Pasteur, in 1904, advocated giving 10-ounce enemata of plain water at a temperature of 100° F. every four or six hours. He claimed that the results were at least as good as with the ordinary nutrient enemata, while it is far simpler, decidedly more bearable for the patient, and does away with the unpleasant and offensive daily wash-out. Sharkey has used $\frac{3}{4}$ pint of saline four times in the twenty-four hours, and has been equally impressed with the advantages of this method. He has made use of it for a week to ten days, but thinks it unwise to continue it longer. If after this one cannot feed by the mouth, he thinks recourse to nutrients is necessary.

I have estimated the nitrogenous output on saline

and on nutrient enemata. It appears to be the same whichever is employed, and follows the course seen in fasting persons. This strongly suggests that the power of utilizing nourishment administered *per rectum* is virtually nil.

Starvation, whether complete or partial, cannot be considered an ideal treatment for an anæmic girl who has recently been further depleted by a large hæmorrhage. Lenhartz has boldly adopted the method of feeding by the mouth throughout, believing that the improvement in the general condition thus produced promotes healing. Concentrated foods rich in albumen are used, so that the hydrochloric acid may be fixed as rapidly as possible by combining with the food protein. Distension of the stomach is guarded against by giving small amounts at short intervals, and by the application of ice to the epigastrium. The patient is fed a teaspoonful at a time, and is not allowed to feed herself for a fortnight. She is kept in bed for three to four weeks, and other medicinal measures, such as the administration of bismuth, can be employed as required.

Essentially the diet consists of iced fresh milk and raw eggs, the whole egg being beaten up and iced. Both milk and egg are prepared in a covered glass tumbler surrounded by ice. The feeding-spoon is also kept iced. Granulated sugar is added to the eggs on the third day; later, raw scraped beef, boiled rice and zwieback, are also given. In America, where the treatment has found an advocate in

Lambert, cooked minced chicken is substituted for the raw ham of the original dietary. Butter is also used largely. Food is given at hourly intervals from 7 a.m. to 9 p.m., but complete rest is allowed at night. The composition of the feeds for the first six days is as follows :

Day.	Eggs. (drachms per feed).	Milk (per diem).	Sugar (per diem).	Scraped Beef (per diem).
1	2	4	—	—
2	3	6	—	—
3	4	8	20 grms. with eggs.	—
4	5	12	20 " "	—
5	6	12	30 " "	—
6	7	12	40 " "	36 grammes in three doses.

These quantities mean that on the first day the patient is taking about two eggs and 6 ounces of milk, while on the sixth day seven eggs and 1 pint of milk are given. These quantities are maintained till the tenth day, when the other things mentioned above may be included, and the routine is gradually relaxed.

The advantages claimed for this treatment are that it is more rapid, and it does not deplete the patient, the food-supply being sufficient throughout. Vomiting and bleeding stop more quickly, and relapse is less frequent, while pain ceases promptly and morphia is never needed ; also it is possible to treat the anæmia earlier.

If these results are confirmed by others, it will mark an important advance in the treatment of gastric ulcer with hæmatemesis, avoiding, as it does, the

misery of starvation and all the discomforts and difficulties of rectal feeding. I have tried it in a fair number of cases, and have been most favourably impressed by it. In one case I thought it best not to continue with it because of some return of pain, and in another there was some return of bleeding which necessitated its abandonment. But bleeding also recurred during the orthodox treatment in this case.

The use of horse-serum has been warmly advocated by Hort and others for gastric or duodenal ulcer. One of the many functions of serum seems to be the restraint it exerts on the autolytic action of the tissue cells. As we shall see in a later chapter, autolysis goes on more rapidly in fasting than in well-fed tissues. This provides a rational basis for the use of horse-serum in a disease for which most methods of treatment entail more or less starvation. The anti-peptic action of serum seems to depend chiefly on the serum-albumen it contains, and Hort has prepared a serum in which this constituent is specially increased in amount. I have employed serum in gastric ulcer, but as it has not been the sole therapeutic agent in any case, I am unable to estimate how much benefit was to be attributed to it; but I believe it to be a useful adjunct to treatment. It can be given in daily doses of 30 to 40 c.c., but it must be fresh and sterile, and should be given directly after food, when absorption is at its height.

Gastro-Jejunostomy. — The surgical treatment of gastric ulcer by gastro-jejunostomy has recently

come so much to the fore that it is worth while to briefly consider some of the principles involved. The success of this operation in overcoming a mechanical difficulty, such as a pyloric obstruction caused by the scarring of an ulcer, is readily comprehensible. But its usefulness is by no means limited to this class of case. Chronic ulceration with recurrent hæmorrhage has also yielded to this treatment. To understand this, we must bear in mind the effect of the hyperchlorhydria associated with gastric and duodenal ulcer. We have seen that one of the actions of the acid when it enters the duodenum is to cause a closure of the pyloric sphincter, which lasts until the pancreatic juice has neutralized it. Excessive acidity provokes excessive contraction, thus keeping the acid in contact with the ulcer, and increasing the pain. But more than this, by keeping the chyme in contact with the pyloric glands the continued secretion of acid is stimulated. Thus a vicious circle is formed: the excessive acidity causes pyloric spasm, while the spasm leads to increased acidity. The most intense pyloric spasm I have ever seen has been in fatal cases of hydrochloric acid poisoning; this is responsible for the invariable occurrence of ulceration and ultimate stenosis in the neighbourhood of the pylorus in the cases that survive long enough.

After gastro-jejunostomy, this hyperchlorhydria almost invariably passes off, though in exceptional cases a jejunal ulcer may follow, showing that the

acidity has persisted. The diminution in acidity results from—

1. Regurgitation of alkaline bile and pancreatic juice into the stomach through the new orifice, which is not provided with a muscular sphincter.

2. Absence of the chemical stimulant to gastric secretion, since the food is no longer kept in contact with the pyloric glands. That the secretion is diminished, and not merely neutralized, is shown by the fact that the total chlorides in the gastric juice are reduced.

In these ways the healing of the ulcer is distinctly promoted. The question has been raised as to the course adopted by the food after the operation. If the pyloric outlet be obstructed, the food must of necessity leave by the new orifice. In one such case on the X-ray screen, I saw the bismuth rapidly pass from the stomach through the new opening into both the afferent and efferent loops of the jejunum. But if there be no obstruction, the food follows its normal course. Legett and Maury got a dog on which this operation had been performed to swallow a bullet to which a string had been attached. The bullet passed out by the new opening, round the duodenum in the reverse direction, and through the pylorus into the stomach again. This it did twice over. Cameron points out that a hard body like a bullet would excite spasm of the pylorus if it approached it from the stomach; and therefore, if it left the stomach at all, it would have to do so by the new opening, but

chyme could still pass out through the pyloric orifice.

The operation does not upset pancreatic digestion, for secretin, the stimulant to pancreatic digestion, can be produced in the jejunum as well as in the duodenum.

Nor does it appear to upset absorption. H. J. Paterson found that nitrogen and fat were absorbed as well as before. According to Cameron, the only exception to this is a slight but definite diminution in the power of digesting and absorbing fat from a purely milk diet. On a mixed diet rich in fat, for the most part in the form of butter, this diminution did not occur. These results were the same whether there was an obstruction at the pylorus or not. He observed the same thing after pylorectomy with an end-to-end anastomosis, where no gastro-jejunostomy had been performed. He explains it by the regurgitation of alkali into the stomach inhibiting the secretion of rennin, and there allowing the uncurdled milk to pass with undue rapidity along the intestine. A difficulty in accepting this view arises from the fact that citrated milk, which cannot curdle, is absorbed as readily by the normal individual as ordinary milk.

According to Hutchison, mucous colitis is not uncommon after gastro-jejunostomy, but no other bad effects have been described.

This operation is, as a rule, much superior to any attempt to excise the ulcer, and, by preventing hyperchlorhydria, it will check any tendency to the

formation of another ulcer. It is indicated in (1) intractable pain, only if accompanied by objective findings; (2) recurrent hæmorrhage; (3) cicatricial stenosis of the pylorus with dilatation of the stomach.

Perigastric Adhesions.—The following case illustrates some of the leading characteristics of perigastric adhesions as a sequel to gastric ulcer, and the physiological considerations on which the diagnosis rests.

A woman of thirty-eight was admitted under my care for abdominal pain, situated just below the costal arch, and a little to the left of the middle line. In the eight years previous she had had several attacks of severe pain after food, accompanied by vomiting. For the past few weeks she had suffered from what she described as a 'different pain,' which was 'dragging' in character, localized, and had no relation to food, but came on as soon as she adopted the erect position. A test-meal showed a total acidity of 0.29 per cent., with presence of free hydrochloric acid. No organisms were found. A skiagram taken after a large dose of bismuth showed that there was no dilatation of the stomach.

Now, although a succession of gastric ulcers may occur in a young woman, an eight years' history of gastric pain and vomiting in a woman of thirty-eight suggests one chronic ulcer that will not heal. But that active ulceration was still present seemed unlikely in the absence of (1) vomiting; (2) any relationship of the pain to food; (3) hyperchlorhydria.

It appeared more probable that the symptoms were due to the result of old ulceration in the form of an adhesion which became dragged upon in the erect posture. Such an adhesion could hardly be in the neighbourhood of the pylorus, for it had led to no dilatation of the stomach. The position of the pain further indicated the fundus as its site.

Paton considers the following points in favour of a diagnosis of perigastric adhesions, all of which were seen in the present case : The symptoms have not infrequently been preceded by those which are more characteristic of gastric ulcer or gall-stone colic. Local tenderness is very frequent; the pain is not uncommonly greatly influenced by the position of the patient; vomiting is not very frequently present, and careful dieting seems to have a very slight effect on the pain and discomfort.

Mr. Gordon Watson accordingly operated, and found a firm adhesion about the size of half a crown midway between the greater and lesser curvatures, and rather nearer the cardiac than the pyloric orifice. On separating this adhesion, it was found that there was a perforation in the centre of an old chronic ulcer, and that the interior of the stomach was in direct contact over a small area with the abdominal wall. The diseased area was invaginated and the stomach closed; the damaged area of peritoneum on the abdominal wall was excised, and the patient made a good recovery.

Dilatation of the Stomach.—It may be well to con-

sider briefly the application of the principles already laid down to the treatment of dilated stomach. We expect to find a steadily increasing discomfort in the intervals between the attacks of vomiting of large amounts. The hydrochloric acid in the test-meal should be diminished if the dilatation be atonic or secondary to malignant disease of the pylorus. It may be increased if an active simple ulcer has produced a stenosis, part of which is doubtless due to spasm; in such a case I have found an acidity of 0·4 per cent. But if the ulcer be healed and cicatricial contractions are alone responsible, the acidity may be normal or diminished. On inspection, the characteristic appearance of 'dropped stomach' may be seen; visible peristaltic waves would be strongly in favour of an obstructive cause. On palpation a succussion splash may be elicited, and a mass felt at the pylorus. Ordinary auscultatory percussion I have not found to be of much service, but the distension of the stomach, by giving a Seidlitz powder in two halves, may render valuable information both on inspection and percussion. It is important to give the alkaline powder first, lest, if hyperchlorhydria be present, additional acid should cause pain. Of all the aids to diagnosis, examination with the X rays after giving $\frac{1}{2}$ to 1 ounce of bismuth oxycarbonate suspended in milk is, in my opinion, the most valuable. In one case of atonic dilatation the bismuth was seen as a meniscus, reaching down to the pubes, for three hours afterwards.

1. *Treatment of Atonic Dilatation.*—Acute dilatation is a dangerous condition of toxic origin, in which treatment appears to be of little avail. Chronic dilatation may exist unsuspected in an alcoholic subject. In the ordinary dyspeptic type there has usually been a long-continued mucous gastritis. I feel that treatment is likely to be very ineffective if lavage be not performed at the outset; otherwise our remedies are apt to be lost in the fermenting slimy mass that is already there. Sodium bicarbonate should be added to the water because of the solvent action of alkalies on mucus. The last part of the fluid employed should have an antiseptic added, such as a drachm of hydrogen peroxide or a weak solution of potassium permanganate. The best diet is one that will not ferment easily. For this reason starchy foods are contraindicated; they should certainly never be given in the form of pap, as is so often done. Dry toast, biscuit, or rusk, are preferable, because in the act of mastication some of the starch will become converted into malt-sugar; but in any form they should be reduced to a minimum. In bad cases I have restricted the diet, at the beginning of treatment, to meat-juices and meat-extracts (because of their stimulating effect on the secretion of hydrochloric acid), and to lightly-cooked minced meat, which does not ferment, and leaves but little residue. From the rapidity with which egg-albumen leaves the stomach it might be imagined that eggs would be a suitable diet in this condition; but patients generally

protest that they cannot digest them. After food, hydrochloric acid or acidol should be given, combined with strychnine, because of its tonic effect on the gastric musculature.

Abdominal massage has been shown to increase the peristaltic waves in the stomach, so that this may prove a useful adjunct to treatment. Rest after meals should be enjoined, since exercise immediately after can be shown to delay the discharge of food from the stomach.

Short has found that in one form of atonic dilatation he obtained the best result by keeping the stomach as empty as possible for three weeks, lavage and nutrient enemata being the means employed.

Operation does not give satisfactory results as a rule. This is, perhaps, not surprising when we remember that regurgitation of alkali occurs into the stomach after gastro-jejunostomy, and in atonic dilatation there is already deficiency of acid.

2. *Treatment of Obstructive Dilatation.*—The only effective means of dealing with this condition is, of course, by operation. The physiological effects of gastro-jejunostomy have already been considered.

Congenital Hypertrophic Stenosis of the Pylorus.

This condition, which is now recognised as a definite cause of vomiting and marasmus in infants, presents interesting problems which bear on the present discussion.

The diagnosis rests upon the combination of vomiting, constipation and wasting with visible peristalsis of the stomach and a palpable pylorus. The symptoms are rarely congenital, the vomiting usually beginning about the fourth week, and not later than the ninth week, after birth. It is generally sudden, copious and forcible, so that a quantity representing more than one feed may be shot out a foot or more from the mouth, and perhaps through the nostrils as well. The frequency of the vomiting is less, while the amount is greater with increasing dilatation. Such symptoms in an infant who has been carefully fed should arouse the suspicion of pyloric obstruction. For the two characteristic signs of visible peristalsis and palpable pylorus, Still lays great emphasis on the importance of examining the abdomen immediately after the infant has been fed. It is at this time, and sometimes only at this time, that the abnormal peristalsis is to be seen, and it is during peristalsis that the thickened pylorus is to be felt. It may be necessary to examine for ten to fifteen minutes before the signs can be elicited. Sometimes the waves appear spontaneously, sometimes only after repeated stroking or gentle kneading of the epigastrium. Still says 'sometimes at one time three bulging eminences are seen like a chain of hills extending across the epigastrium. They move so slowly that at times they may even be seen to pause altogether, but each in turn fades away in the right hypochondrium.' The thickened pylorus

can be felt at intervals on palpation just outside the right nipple line, and about one-third of the distance between the umbilical level and the costal margin. It may be excited to contract by gentle kneading with the tips of the fingers pressed deeply into the abdomen in this situation.

According to Miller and Willcox, the contents of the stomach show, as a rule, a marked increase in the ferment activity, together with excessive secretion of mucin. The total acidity is variable, but tends to be below normal, presumably varying inversely with the amount of gastritis present.

Post-mortem, the stomach is found to be greatly dilated, and the pylorus is much thickened for about $\frac{1}{2}$ inch, yet a probe can usually be passed through it readily. The thickened pylorus protrudes into the duodenum in a manner which recalls the protrusion of the cervix uteri into the vagina. Microscopically, a genuine increase in the muscular tissue can be made out, and nothing else.

The pathology of this condition is a vexed question. **Congenital stenosis** would appear to be a misnomer, since the hyperplasia occurs after birth, and there is no true narrowing of the lumen. Pyloric spasm leading to muscular hypertrophy seems to be the sequence of events. But what causes the spasm?

In adults the most fertile cause of such spasm is hyperacidity, but this is not found in the form now under discussion.

Miller and Willcox think that the excess of rennin may play a part by causing a large curd to form rapidly in the stomach, which would excite pyloric spasm by its bulk. They call attention to an acid dyspepsia in infants which provokes pyloric spasm without hypertrophy. It occurs in infants over three months old; there is hyperchlorhydria, no mucin, and but little ferment, in the stomach contents; no pyloric tumour can be felt. If this be so, it follows that there must be some other factor in the production of the hypertrophy besides pyloric spasm. John Thomson suggests that it is due to a muscular inco-ordination of the muscles of the stomach, the central nervous system having not yet acquired proper control. On this view it is comparable to the stuttering of a child who is learning to talk.

Treatment.—This will have to be prolonged, and will call for much patience on the part of all those concerned. It is important to give only small quantities of thin food, so as to avoid any distension of the stomach and any residue. At first whey and raw-meat juice only should be given. The amount at each feed should be a teaspoonful every twenty minutes at the outset, and this should be only slowly increased to two, three, or four teaspoonfuls at longer intervals. If milk be used, it should be citrated to prevent curdling. Some observers are in favour of stopping all food by the mouth for a time; they believe that this enables the spasm to subside. But diet alone is hardly likely to lead to success. System-

atic lavage must also be employed. Still's plan is to have the stomach washed out just before a feed twice daily for several weeks, and then once daily for several weeks longer, with a solution of sodium bicarbonate (2 grains to the ounce) through a Jacques' soft catheter, No. 12 or 14. This must be continued until not only the vomiting has stopped, but till the weight is steadily increasing.

Minute doses of opium ($\frac{1}{80}$ minim of the tincture) have been recommended by Newman Neild as helping to overcome spasm.

Operation was strongly advocated till recently; Cautley and Dent have had several successful cases thus treated. Forcible dilatation, pyloroplasty and gastro-enterostomy, are the various methods that have been employed. But they all have grave risks, both at the time from shock, and subsequently from the diarrhœa which so often follows. This is probably due to the atrophic intestine, which is unable to deal with any large amount of food after the obstruction has been removed. 'The infant's life hangs in the balance for several weeks after operation.' This being so, we should not resort to surgery until it is clear that lavage and dieting will not relieve the vomiting and the wasting.

APPENDIX TO CHAPTER II

The Examination for Hydrochloric Acid in Gastric Contents.

That doubts are so often thrown on the value of a chemical examination of the gastric contents is due in many cases to the fact that defective methods have been employed. It is not sufficient to test qualitatively for free hydrochloric acid, and then take the total acidity as a measure of the physiologically active hydrochloric acid.

The test-meal I have generally employed is $\frac{3}{4}$ pint of tea without milk or sugar and a round of dry toast. It may be urged that this would be a very feeble excitant of gastric secretion, but it is quite satisfactory, in my experience, for a series of comparative tests. Indeed, so far from not causing secretion, this meal is apt to be digested by the end of an hour, and lately I have only allowed half an hour between the meal and using the stomach-tube.

As a qualitative test for detecting free hydrochloric acid, Gunzberg's still holds its own as the most reliable. Willcox urges the importance of having the reagent quite fresh, as it loses its delicacy in a few hours. He says: 'The best way of applying the test is to keep the phloroglucin and vanillin in bottles to the corks of which are attached little scoops which will measure about 4 grains of the former and 2 grains of the latter. These quantities are placed in a dry porcelain evaporating-dish with 1 c.c. of alcohol (pure methylated spirit does quite well), and then about 2 c.c.

of the filtered gastric contents are added. The dish is heated on the water-bath till its contents are nearly dry. A brilliant scarlet-red colour indicates free HCl; a yellow colour is negative.'

Total acidity is determined by titration with a decinormal alkali, using phenol phthalein as an indicator.

The amount of physiologically active hydrochloric acid is the most important point, and this can best be determined by Willcox's method. The principle of it is as follows: In the gastric contents hydrochloric acid may exist in three forms—

- | | | | | |
|---|-----|-----|-----|------------------------------|
| 1. Free HCl | ... | ... | ... | } Physiologically
active. |
| 2. Combined HCl: | | | | |
| (a) With proteins and nitro- | | | | |
| genous organic bases ... | | | | |
| (b) With inorganic bases, as sodium chloride. | | | | |

It is not necessarily the case that the presence of free HCl is of more importance than that of the combined acid. The latter, which is combined with protein and nitrogenous organic bases, is acid that was free a short time before, but has now begun its duties in the process of digestion; it is, therefore, of equal importance with free HCl. The HCl combined with inorganic bases need not be considered.

Now, if we estimate the total chlorides in a sample of gastric juice, and in another estimate the chlorides present after charring—*i.e.*, the inorganic chlorides—the difference between these two results gives the amount of physiologically active HCl.

The estimation is carried out as follows : 'Two equal volumes of the filtered gastric contents (20 c.c.) are taken.

'(a) One portion is diluted with about 40 c.c. of distilled water, 10 c.c. pure nitric acid added, and about 5 c.c. of solution of iron alum. A measured excess (80 c.c.) of decinormal silver nitrate solution is added. Decinormal ammonium sulphocyanide solution is run in from a burette until a permanent reddish-brown tint just results. The difference between the quantity of silver nitrate solution added and the ammonium sulphocyanide solution used gives the amount of total chlorides present as decinormal hydrochloric acid.

'(b) The other portion of the gastric contents (20 c.c.) is placed in a porcelain evaporating-basin, $4\frac{1}{2}$ inches in diameter, and evaporated to dryness on a water-bath; the solid residue is heated for about an hour on the water-bath, and the dish is then placed on a piece of wire gauze and heated with a small Bunsen flame, the flame not coming into actual contact with the basin. The heating is continued for about ten minutes until the residue is well charred. The dish is cooled, about 60 c.c. of water and the pure nitric acid are added, the contents being well stirred with a glass rod. The titration is performed exactly as in (a), and the quantity of chlorides present is given in terms of decinormal hydrochloric acid. The difference between the chlorides present in (a) and (b) expresses with great accuracy the amount of the physiologically active HCl.'

[For a fuller account of methods, see Willcox, Transactions of the Pathological Society, vol. lvi., p. 250; and Harley and Goodbody, 'Chemical Investigation of Gastric and Intestinal Diseases' (Arnold).]

CHAPTER III

THE WORK OF THE PANCREAS

ALTHOUGH the pancreas provides the most active digestive secretion in the body, and plays an important part in general metabolism, it is still true that disease of this organ is rarely recognised during life. A consideration of the way in which the pancreas does its work may enable us to realize the difficulties attending this recognition, and the steps by which they are being overcome.

As soon as the acid chyme enters the duodenum the secretion of pancreatic juice begins. Its alkalinity corresponds almost exactly to the acidity of the gastric juice, so that, allowing for the alkaline bile, the total bulk of pancreatic secretion will be rather less than that of the gastric secretion.

Von Mering has shown that injection of acid into the duodenum leads to closure of the pyloric orifice. Not until this acid has been neutralized by the pancreatic juice it has produced can more of the acid contents of the stomach pass through the pyloric sphincter. In this way the secretion is exactly regulated to the amount of food arriving from the stomach.

Pawlow thought that the acidity of the chyme acted by stimulating special nerve-endings in the duodenum, but Wertheimer showed that the acid was equally effective after section of all the nerves in the neighbourhood, or even after extirpation of the solar plexus. The acid produced less effect the further down the intestine it was introduced, until within two feet of the ileo-cæcal valve it ceased to have any effect at all. This paved the way for Bayliss and Starling's important discovery that the hydrochloric acid of gastric juice, when it comes into contact with the mucous membrane of the intestine, leads to the production of a chemical stimulant, *secretin*, which is absorbed from the cells by the blood-stream and carried to the pancreas, where it acts as a specific stimulant to secretion.

It may be well to recall how this result was arrived at. Dilute hydrochloric acid was placed in a loop of jejunum which had been previously isolated from the rest of the body except for its blood-supply. The absorption of acid was accompanied by a secretion of pancreatic juice. If, however, the acid were injected direct into the blood-stream, it was ineffective. On the other hand, a saline extract of the intestinal mucosa treated with hydrochloric acid and injected into the blood-stream produced an active secretion. Thus, for pancreatic secretion to occur normally, hydrochloric acid must descend from the stomach, which will only happen in the presence of food.

It is generally conceded now that this chemical mechanism is sufficient to account for all the facts of pancreatic secretion. Clayton-Greene has, however, recorded a case which he believes to point to a nervous control. During pylorectomy for malignant disease of the stomach a pancreatic fistula was accidentally formed. A few seconds after food was swallowed pancreatic juice began to appear, and this might even occur when the food had only been seen and not swallowed. Nervous mechanisms are, we know, distinguished from chemical by the speed with which they act. Certainly in this case the reaction was extremely rapid, but we must not forget that all attempts to discover the channels by which such nervous impulses could pass have failed.

At any rate, we may safely assert that after severance of all nervous ties secretin can produce a copious flow of pancreatic juice, while without due secretion of acid adequate pancreatic digestion is impossible. Comprehension of this chemical factor brings the regulation of pancreatic digestion much more under our control.

Inadequate pancreatic secretion appears to have a most striking effect upon the growth of the body. Byrom Bramwell has described a condition of persistent infantilism as a result. A lad of eighteen, who did not look more than eleven, came under his observation. He was perfectly formed, bright, and intelligent. His height was 4 feet 4 inches, and his weight 4 stone $7\frac{1}{2}$ pounds. He had suffered from

chronic diarrhœa for nine years. The abdomen was swollen and tympanitic. Skiagrams showed that the epiphyses, which should have united between sixteen and eighteen, had not done so. There was no glycosuria. The pancreatic secretion was found to be defective or absent by tests described later. Under treatment by a glycerine extract of the pancreas a very marked improvement occurred. The diarrhœa was greatly diminished; he grew $5\frac{3}{4}$ inches in two years, and increased 1 stone 8 pounds in weight, although previously he had not grown for eight years. He developed signs of puberty, till then entirely lacking.

Here profound disturbances resulted from pancreatic inadequacy, yet there was no glycosuria, suggesting that it was only the external secretion of the pancreas, and not its internal secretion, that was at fault. Other such cases have been described since. A few years ago I saw a case of severe congenital syphilis in a boy of sixteen, combined with persistent infantile features. In appearance he looked about eight or ten years old, and all signs of puberty were lacking. Now, congenital syphilis is known to lead to arrested bodily development, but the special feature of interest here was the existence of fatty diarrhœa, suggesting pancreatic inadequacy. At the post-mortem examination, the condition of the pancreas typical of congenital syphilis was found. As in all these cases, there was no glycosuria.

Why does not the pancreas digest itself? It was

long a standing problem in physiology why the digestive organs themselves, composed of protein tissues, should resist processes capable of digesting other proteins. In the case of the stomach, the fact that the juice could only act in an acid medium, while the blood was alkaline, was held to explain the difficulty. But then this only made the case of the pancreas all the more striking. Now, however, we are provided with a satisfactory answer to the riddle. The tryptic activity of the pancreas is hedged around with some remarkable safeguards.

1. *Active trypsin is normally only liberated in the presence of food.* As we have seen, hydrochloric acid is the stimulant to pancreatic secretion, and this will only pass into the duodenum as the result of food leaving the stomach.

Moreover, fresh pancreatic juice contains inactive trypsinogen. Before this can become active trypsin, it must be acted upon by another ferment, *enterokinase*, which appears to be present only in the *succus entericus*. Therefore the fluid present in the duct of *Wirsung* cannot possibly injure the gland, for it is inactive until discharged from the papilla. And although any mechanical irritation of the intestine will lead to the outpouring of mucus, true *succus entericus* is only secreted in the neighbourhood of the food; while its richness in enterokinase depends on the stimulating presence of the pancreatic juice according to Pawlow. Whatever the exact stimulus to *succus entericus* may be, it is difficult to extract

enterokinase from the intestine of a fasting animal, so that its presence seems to be dependent on the food. By this 'double locking' it is insured that under normal conditions active trypsin can only be liberated in the presence of food.

The importance of these safeguards is seen on injecting secretin into fasting dogs. Under these experimental conditions active pancreatic juice is set free, and the intestinal walls are extensively digested.

2. *Trypsin is an unstable body, and rapidly destroys itself, if proteins or their products are not present.* In this way the surplus trypsin left over at the end of digestion is soon disposed of.

3. *The blood-serum contains an antibody to trypsin,* thus destroying any of the ferment which might have become accidentally introduced into the circulation.

Trypsin is no exception to the general rule that the introduction of a substance of the protein class into the circulation will lead to the formation of the appropriate antibody. It is interesting to note that intestinal worms also contain an antitrypsin. This will explain at once their power of living in the intestine and the voracious appetite of their host, who is thus largely incapacitated from assimilating proteins.

For these reasons it is difficult to understand how pancreatic hæmorrhage or necrosis can be due to self-digestion of the gland by trypsin. But the question arises whether other things besides enterokinase may

be capable of activating trypsinogen. After all, a ferment merely carries out with great velocity, and at the temperature of the body, a reaction which is capable of being performed, though much less readily, by other means.

Delezenne claims that calcium salts can activate trypsinogen, as we know they can render fibrin ferment active. A pre-existent pancreatic catarrh might lead to the formation of active trypsin within the ducts of the gland; pancreatic calculi, for instance, are rich in calcium salts. Guleke believes self-digestion by trypsin to be the cause of the toxic symptoms in acute necrosis of the pancreas. He produced similar symptoms by transplanting the pancreas of one dog into the peritoneal cavity of another, and the same constitutional effects by intravenous, intra-peritoneal, or subcutaneous injections of trypsin. The animal could, however, be partially immunized against the effects of transplantation by injections of gradually increasing doses of trypsin.

Barnard met with a case in which laparotomy for a ruptured pancreas was rapidly followed by digestion of the rectus abdominis in the neighbourhood of the wound. Yet no injury to the duodenum was found at the necropsy, so that there could hardly have been activation by enterokinase.

The drainage of pancreatic cysts, too, has occasionally been followed by extensive self-digestion along the track of the fluid.

But such cases are exceptional, and Mayo Robson

is probably correct in referring the usual cause of the necrosis to the passage of infected bile back along the pancreatic duct. Normal bile will not activate trypsinogen, so that the effect is most probably due to some septic infection of the bile. It is now generally agreed that the best treatment for inflammatory conditions of the pancreas is drainage of the gall-bladder, so as to prevent infected bile from coming into contact with the inflamed tissues.

Fat Necrosis.

With regard to steapsin the case is different; should the juice be extravasated from the gland, digestion of the body-fat will follow. 'Fat necrosis' is due to this splitting of the body-fat into glycerine and fatty acid, the latter combining with lime salts. Flexner has demonstrated the presence of steapsin in the affected areas, while Opie was able to show its presence in the urine in one such case by its decomposing action on ethyl butyrate.

These opaque white areas, often surrounded by a ring of inflammation, are usually most abundant in the neighbourhood of the pancreas and omentum, which suggests that they are caused by direct extravasation of the steapsin.

Cambridge's 'pancreatic reaction' was founded originally on the idea that the glycerine, which would be set free from the fat in fat necrosis, reappeared to some extent in the urine, where it could be converted into a sugar and made to yield crystals with phenyl

hydrazine. The form and solubility of these crystals gave valuable evidence, he believed, as to the existence of pancreatic disease and its nature.

His methods and conclusions were seriously questioned, and, speaking generally, other observers did not appear to get the diagnostic results claimed for this reaction. He has since abandoned the idea that the source of the sugar is the glycerine, as it is found to be a pentose. Relatively there is a large proportion of a pentose-yielding substance in the pancreas, so that in disintegration of this gland we might expect to find it in the urine. The pentose is set free from some antecedent body by heating with dilute acid. Not only will the pentose yield crystals with phenyl hydrazine, but glycuronic acid will do so also. Cammidge has recently introduced an improved or 'C-reaction,' which depends on precipitating the glycuronic acid by tribasic lead acetate after the preliminary treatment with hydrochloric acid. On now heating with phenyl hydrazine, crystals of a pentosazone will be obtained free from other crystals. As disintegration of other glands might yield small amounts of pentose, it is not claimed that the reaction is pathognomonic of pancreatic disease. In 250 consecutive cases, however, he obtained the following results by this method :

			Number.	Positive.	Negative.
Acute pancreatitis	2	2	0
Chronic pancreatitis	65	65	0
Cancer of pancreas...	16	4	12
No pancreatitis	117	4	113
Normal	50	0	50

These figures are certainly striking, and if the results are confirmed, the method should prove a valuable addition to our means of diagnosing pancreatitis. Already Eichler has obtained this reaction in the urine of three dogs in which he had produced an experimental pancreatitis.

Other Pancreatic Ferments.

Pancreatic juice can act on all three classes of food-stuffs. The starch-splitting ferment, amyllopsin, only differs from ptyalin in saliva in being more rapid and in being able to act on unboiled starch. Were amyllopsin to enter the circulation, it could do no harm beyond digesting the glycogen in the liver. This could not account for pancreatic diabetes, since the glycosuria does not cease with the emptying of the glycogen reservoirs, and is most intense after total excision of the pancreas.

Pancreatic juice also contains small amounts of erepsin, which completes the digestion of proteins, a milk-curdling ferment and a malt-sugar-splitting ferment. But they are of subsidiary importance here, being more abundantly present in other digestive secretions.

Adaptation of the Pancreatic Secretion.

From work done in Pawlow's laboratory remarkable conclusions were reached as to the way in which the pancreatic juice was adapted to the character of the food. Thus, a meal of bread was thought to cause a

secretion of juice rich in amylopsin, but very poor in the fat-splitting ferment, while milk excited a juice rich in this latter constituent. But this was before the existence of enterokinase was known, and we realize now that the amount of trypsin found must have varied with the time allowed for the conversion of trypsinogen by enterokinase to occur. Wohlgemuth, observing a patient with a pancreatic fistula, found the greatest amount of secretion after a carbohydrate meal, fat causing the least secretion, while protein was intermediate in its effect. But we must remember that bread requires a very large secretion of gastric juice, while fat actually inhibits the secretion. Therefore, the amount of pancreatic juice varied directly with the amount of acid passing from the stomach into the duodenum; in other words, it depended on the amount of secretin formed. This is a very different thing from a variation in the proportion of the ferments in the juice, which was what Pawlow thought occurred.

According to Weinland, the pancreatic juice of new-born puppies does not contain lactase, though this ferment, which is capable of splitting up milk-sugar, makes its appearance in the juice a few days after birth. He believed that lactase is normally absent from the pancreatic juice of adult dogs, but is found there if the animals are fed on milk for two or three weeks. Bainbridge obtained similar results, and thought that the intestinal mucosa was the place where the adaptation occurred, a new substance being

formed there, which was carried in the blood-stream to the pancreas, exciting the production of lactase.

This seemed to bring digestive ferments into line with 'antibodies,' the contact of a food-stuff with the tissues resulting in the production of something that broke up that particular food-stuff. Now, pancreatic juice normally contains no amylopsin in infants during the first few months of life. Considering the diet of many of the children of the poor, we might have expected them to acquire quite early a ferment capable of digesting starch. Or, to take a more extreme instance, had Nebuchadnezzar only continued to eat grass like an ox, he should have acquired the power also of digesting it like an ox.

But such tempting hypotheses received their death-blow when Plimmer showed that faulty methods had been responsible for these results, and that no lactase could be developed in this way. Indeed, as lactase is a normal constituent of the intestinal mucosa, its development by the pancreas is not necessary for the well-being of the organism. Nor is it easy to see how it could arise; a special lactase-secretin would be necessary, whereas everything points to secretin being a definite chemical entity which stimulates all the ferments alike in pancreatic juice. We may conclude with Starling that the one definite case in which qualitative adaptation of the pancreatic secretion to the food was thought to occur is disproved.

The Influence of the Pancreas on General Metabolism.

Since the classical experiments of von Mering and Minkowski, much interest has been taken in the relationship of the pancreas to diabetes. To recall their results briefly. Extirpation of the pancreas in dogs is followed within twenty-four hours by glycosuria, reaching its maximum on the third day, when it amounts to 8 or 10 per cent. on a carbohydrate-free diet. This is associated with excess of sugar in the blood, and the presence of acetone in the urine. The constancy of the ratio of the carbon to the nitrogen excreted (2·8 to 1) is best explained by supposing that protein is the source of this sugar. Though glycosuria does not follow an ordinary diet if $\frac{1}{8}$ to $\frac{1}{12}$ of the gland is left, it does if any excess of carbohydrate be given. This portion of the gland can still exert its control even if its connection with the duodenum be severed.

These facts have been variously explained as follows:

1. *The pancreas may furnish an internal secretion to the blood or lymph which is necessary for normal metabolism; either—*

(a) A glycolytic ferment which breaks down the sugar into some simpler form in which the tissues can use it, or—

(b) An amboceptor which, by linking the sugar on to larger molecules such as protein, prevents the escape of the relatively small molecules of sugar by the urine.

2. *The pancreas may destroy some toxic product absorbed from the alimentary canal which hinders the normal assimilation of sugar.*

Allied to this is the view of Schmiedeberg, who holds that in diabetes glucose is combined in the blood in some inert compound which prevents its assimilation by the tissues.

To assume the existence of an internal secretion of the pancreas is certainly the easiest way of accounting for the phenomena of pancreatic diabetes; but we must remember that it is an assumption. No such secretion has ever been isolated, nor have pancreatic extracts allayed glycosuria in any way.

As the internal secretion passes into the circulation, and as the muscles are the great site of carbohydrate consumption, it is possible that the secretion must be further modified by the muscular tissues. Otto Cohnheim claimed that, whereas extracts of pancreas and of muscle had no glycolytic action separately, mixtures of such extracts led to an enormous disappearance of sugar from its solutions. Blood-serum had an inhibitory effect on this reaction. Bacterial action was excluded. He concluded that muscle contains a sort of zymogen or inactive ferment, which is rendered active by the pancreatic internal secretion, just as enterokinase makes trypsinogen active. Croftan thought that clinically glycosuria could be alleviated by a mixture of pancreatic and muscle extracts with hæmoglobin.

But unfortunately these experiments, which pro-

mised so well as an explanation of some of the difficulties in the pathology of diabetes, have not been confirmed by other observers, who failed to get any such results.

Another possibility presents itself. In diabetes it might well be that it is not so much the pancreas which is at fault as that the stimulant to its action is missing. Secretin might be the stimulant to the internal as well as the external secretion. Spriggs tried intravenous injections of secretin without avail in a case of diabetes, however. Moore, Edie, and Abram believed that by giving secretin by the mouth they were able to get good results in diabetes. This seems unlikely, since Starling found that in animals secretin is not absorbed when introduced even in large amount into the alimentary canal. Beddard and Bainbridge were unable to see any improvement in their cases under this treatment, and critically reviewing Moore's cases, they concluded there was not sufficient evidence that the secretin was responsible for the improvement that occurred.

Moreover, in a typical case of mine of diabetic coma, Bainbridge was able to find pro-secretin abundantly present in the duodenal mucosa; and this was only one of a series in which pro-secretin was so found. Therefore there is no reason to consider that diabetes is in any way due to the loss of the hormone to pancreatic activity. If it were, it would necessarily be accompanied by signs of inadequate pancreatic digestion, which are certainly not usually observed.

The causation of glycosuria will be more fully considered in a later chapter.

The Meaning of the 'Cell-Islets.'

The 'cell-islets' described by Langerhans in the pancreas have been regarded by many as the source of this internal secretion. These ovoid groups of shrunken, poorly staining cells are apparently developed from the secreting alveoli, with which in reptiles they remain continuous. In man, delayed development, in consequence of congenital syphilis, for instance, may lead to persistence of this embryonic continuity. Normally they contain no ducts, and are supplied with wide tortuous capillaries or 'sinusoids.' In man they are scattered irregularly through the gland, though in some animals, such as the cat, they are constantly in the centre of the lobe. Rennie found very large islets in the bony fishes, including in some a principal islet, separated from the rest of the organ, visible to the naked eye, and capable of dissection.

Opie is a strong supporter of the view that, when diabetes is the result of pancreatic disease, injury to these islets is responsible for the disturbance of carbohydrate metabolism. He claims that the more selective the influence of a lesion is upon the islets, the more likely is it to cause diabetes. Thus interstitial pancreatitis may be interlobular or interacinar; the latter soon affects the islets which lie deep within the lobules, whereas the former has to be far advanced

for the islets to become involved. Corresponding to this, he finds the interacinar form is much more frequently associated with glycosuria than the interlobular. Hyaline degeneration, too, which he describes as particularly liable to affect the islets, he believes to be specially apt to produce glycosuria. .

On the other hand, Dale has advanced strong reasons for believing that these islets do not represent fixed and permanent structures in the gland, but are being continuously formed from secreting alveoli. By injection of secretin he has been able to imitate the normal stimulation of the pancreas, and yet to carry it to a pitch of exhaustion of which previous methods would not allow. As a result he finds islets of such abundance and of such a size as are never seen in any part of a resting gland. Moreover, they show signs of active formation. Apart from large areas of definite islet tissue, a considerable proportion of the remaining alveoli show partial change, some cells having lost their normal staining properties, and having become assimilated to centro-acinary cells. There is frequently apparent continuity of the islets with the epithelium of the smaller ductules. The proportion of islet tissue to secreting tissue is also increased by prolonged fasting—*i.e.*, the disappearance of the stored material, whether by discharge from the duct or by absorption into blood or lymph when nutrition fails, is attended by increased formation of islet tissue.

He concludes that the islets are not independent

structures, but are formed by certain definite changes in the arrangement and properties of ordinary secreting cells, bringing about a reversion to embryonic type.

A study of Dale's microphotographs is certainly very suggestive, showing as they do all transitional forms between alveoli and islets. Indeed, ordinary cell-islets, when prepared by Heidenhein's method, produce a distinct impression of badly staining shrunken alveoli that have lost their normal arrangement. It is, however, rather difficult to understand why they should be found in a different position in different animals, if produced in all alike by breaking down of ordinary alveoli.

After all, the nature of the islets does not really settle the question of internal secretion. If this exists, it does not necessarily require special cells to elaborate it. In the liver, we do not find certain bile-producing cells and other glycogenic cells, but all the cells seem equally concerned in both the internal and external secretions of the gland. Noel Paton points out that, while the cell-islets are well developed in the duck, the pancreas plays no important part in regulating the metabolism of sugar, for excision of the pancreas does not cause glycosuria in them. This throws doubt on the hypothesis that their function even in mammals is to regulate carbohydrate metabolism. Though cell-islets are increased by injections of secretin, such treatment has not alleviated diabetes. Rennie and Fraser fed diabetics with the principal islets of fishes, but the results were inconclusive.

To recapitulate. Though total excision of the pancreas causes glycosuria on a carbohydrate-free diet, and partial excision results in alimentary glycosuria, there is no conclusive evidence that the cell-islets are the site of formation of the internal secretion which regulates carbohydrate metabolism, or that they form an antitoxin to a body which would otherwise cause glycosuria. Normally formed from the alveoli, they remain in connection with them under conditions of retarded development, and their formation from alveoli is greatly increased in the exhausted or starved gland.

The Manifestations of Pancreatic Disease.

Disease of the pancreas is still considered to be rare, but in view of the multifarious duties of the gland, it would be remarkable were this really the case. Gross lesions may be rare, but inflammatory changes are not uncommon. 'Catarrhal jaundice' is often pancreatic in origin, and it is probable that in many cases of intractable dyspepsia the pancreas is at fault.

Three main factors tend to obscure the diagnosis of pancreatic disease:

1. 'Disease of the organ is seldom uncomplicated, but is usually consequent on changes in the duodenum, liver, or bile-passages' (Opie); and when not the result of such changes, it may be the cause of them.
2. The digestive work of the pancreas can largely be carried out by other secretions. Digestion of fat

has been thought to be an exception to this statement. But it has now been shown by Volhard, and more fully by Stade, confirmed by Edkins, that even under aseptic conditions the gastric juice is capable of splitting 50 to 60 per cent. of the fat of the food into fatty acid and glycerine. This accounts for Abellmann's observation that, after excision of the pancreas in dogs, 53 per cent. of the fat of milk is still digested, and for Hédon's and Ville's, who found that 50 per cent. of fat was digested after the pancreatic juice was prevented from reaching the intestine. Moreover, fat-splitting can be accomplished by intestinal bacteria to some extent.

Another source of fallacy is that occlusion of the main pancreatic duct may be partially compensated for by the duct of Santorini.

On the other hand, it must be remembered that occlusion of the bile-duct, or alimentary tuberculosis, may result in excess of fat in the stools without pancreatic disease.

3. Pancreatic disease is only one of many causes of glycosuria, and lesions which only affect part of the gland may not be accompanied by glycosuria at all.

Bearing these sources of error in mind, we may now consider—

The Signs of Pancreatic Inadequacy.

1. *Defective External Secretion* as indicated by—

(a) *Failure of Tryptic Digestion.*—Unaltered muscle fibres may be found in the fæces after a meat

meal. A more delicate sign according to Byrom Bramwell is this: On a milk diet the amount of phosphoric acid in the urine is greatly below the normal; after administration of pancreatic extract the amount of phosphoric acid is markedly increased. The reason for this appears to be that on a milk diet caseinogen is the main source of phosphoric acid in the urine. In the stomach this is broken up into paranuclein and a proteid. Paranuclein, which contains 4 per cent. of phosphorus, is insoluble till it comes into contact with trypsin, which splits it up further.

Sahli recommended the following test: Gelatin capsules hardened in formalin are almost unaffected by gastric juice, but are dissolved by trypsin. He states that if such capsules are filled with iodoform and swallowed, the saliva and urine should contain iodides and iodates, which may be tested for by chloroform and nitric acid; the nitric acid sets free the iodine, which gives a pink colour to the chloroform. Provided that the mobility of the stomach is normal, absence of this reaction, four to eight hours after swallowing the capsule, shows that tryptic digestion is impaired. In such cases administration of 2 drachms of liquor pancreaticus two hours after the capsule will lead to appearance of the reaction an hour later.

In common with most others who have tried it, I have found this test very unsatisfactory. If the capsules are not hardened enough they may be

digested in the stomach, while if they are hardened too much, as is more commonly the case, no reaction is obtained even though the pancreas is healthy, because the capsule now resists tryptic digestion also.

(b) *Failure of Starch Digestion*.—Though ptyalin can digest boiled starch, amylopsin alone can digest unboiled starch grains. Abelman found 20 to 40 per cent. of the starch in the fæces after experimental excision of the pancreas.

(c) *Failure of Fat Digestion*.—This may result in true steatorrhœa, or in the presence of fat droplets, fatty acid crystals, or soap in the fæces in such amounts as can only be detected by the microscope. But a quantitative estimation is necessary to determine the excess of fat satisfactorily. Cammidge's method (*Brit. Med. Journ.*, October 28, 1905) has the advantage that it allows of the determination of the total fat, and the proportions that are saponified and unsaponified. In normal fæces the saponified and unsaponified fats are approximately equal in amount. Now, the pancreas provides for the fat-splitting that must precede saponification, so that if the excess of fat in the stools is due to a pancreatic defect, unsaponified fat will be in excess of the saponified. On the other hand, the bile-salts provide for the absorption of the fat already digested by the pancreatic juice, so that if the excess of fat be due to loss of bile simply, the saponified fats will be in excess, because they cannot be adequately absorbed.

In the former case the fatty stools can be con-

trolled by the administration of pancreatic extract, as was proved by Langdon-Down in 1869.

According to Cammidge, an additional diagnostic point between jaundice originating from gall-stones and that resulting from new-growth of the head of the pancreas is that the obstruction is much more complete with new-growth. Consequently stercobilin is completely absent from the fæces in malignant disease, whereas in obstruction of the biliary passages by gall-stones some stercobilin can nearly always be found, although the fæces may appear quite white to the naked eye.

2. *Defective Carbohydrate Metabolism.*—Though glycosuria may be absent in pancreatic disease, it may often be excited by an excessive carbohydrate diet. Thus, Wille tested a large number of patients with various diseases by administering 70 to 100 grammes of dextrose dissolved in $\frac{1}{2}$ litre of tea or coffee. The urine was passed just before, and was then tested at intervals of two hours. If alimentary glycosuria exists, sugar should be found at the end of two hours. It should be remembered that a normal individual can take about 200 grammes of dextrose before glycosuria occurs.

Wille found that, of fifteen cases of alimentary glycosuria thus tested, which he was able to follow to necropsy, ten had grave lesions of the pancreas. Though alimentary glycosuria may occur in other conditions, such as hysteria, exophthalmic goitre, and chronic alcoholism, it remains a sign of considerable

diagnostic value. A negative result does not exclude pancreatic disease, for as long as sufficient tissue remains to form the internal secretion this symptom will be lacking. Our treatment must be directed towards removing the cause before glycosuria has occurred. It should be regarded as a late symptom, and one that makes the prognosis much more serious.

3. *Signs of Pancreatic Disintegration.*—Cambridge's pancreatic reaction would fall under this head, as the source of the pentose obtained from the urine is thought to be the pancreatic cells breaking down as the result of inflammatory change. The presence of the reaction in 25 per cent. of the cases of pancreatic cancer is explained by the frequency of associated inflammatory changes.

Mayo Robson sums up the relative significance of these signs as follows :

'The presence of an excess of fat in the motions, in the absence of jaundice and diseases of the intestine, is suggestive of pancreatic diseases. If azotorrhœa is found along with steatorrhœa, it is almost certain that the pancreas is diseased, and if the pancreatic reaction in the urine (Cambridge), diabetes, and an epigastric tumour be present, the diagnosis is certain.'

Trypsin and Cancer.

This is perhaps the most convenient place to refer to the treatment of cancer by pancreatic ferments, of which so much has been written lately in the lay press.

This treatment has been advocated by Beard on the following grounds: He considers that alternation of generations occurs throughout the animal kingdom as it does in the vegetable. Thus the fertilized ovum does not at once give rise to the next generation, but forms an asexual trophoblast, from one cell of which the new generation will arise. But the other cells of the trophoblast have the power of multiplying also, and these cells tend to invade the tissues of the new individual. At a certain 'critical period' in development, which in human beings occurs at the seventh week, these trophoblastic cells begin to degenerate and disappear. This corresponds to the stage at which the pancreas begins to show signs of activity, which suggested to him that the activity of the pancreas was responsible for the destruction of the trophoblast.

Now, it is well recognised that the cells of the chorion may occasionally initiate a malignant growth in the uterus, the so-called chorio-epithelioma. Such a growth is composed of cells which are indistinguishable from the trophoblastic cells.

He believes that this occurs in cases where, owing to the death of the embryo before the critical period,

the foetal pancreas does not perform its function. The foetus is expelled, leaving its chorion behind to go on multiplying unchecked.

Barbera found trypsinogen and enterokinase in foetal dogs, where there would be no food to digest. Beard explains this on the ground that the trophoblast would require to be digested at this period.

One form of malignant disease is composed of cells indistinguishable from trophoblast, and all malignant disease has the characteristic trophoblastic feature of capability for asexual multiplication to an indefinite extent. It is, in fact, due to trophoblastic cells left in the body which have not been destroyed by pancreatic ferments, and have now taken on active growth.

Just as trypsin is capable of destroying normal trophoblastic cells, so it has a specific effect in destroying cells of malignant disease; but it is stated to have no effect on the normal cells of the living body.

This difference is explained thus. Alternation of generations is accompanied by a difference in stereochemical structure. The tissues of the sexual generation in animals are composed of lævorotatory proteins and dextrorotatory carbohydrates, while the asexual trophoblast and its direct descendant, cancerous tissue, are composed of dextrorotatory proteins and lævorotatory carbohydrates.

The reverse is the case with plants, but here it is the asexual generation which forms the conspicuous

structure, while the sexual generation is small and inconspicuous—*e.g.*, the prothallus of the fern.

The animal can only assimilate food-stuffs of similar stereo-chemical configuration to its own tissues, and it produces ferments, such as trypsin, which are antagonistic to bodies of the opposite configuration. Therefore the lævo-albumins of the living body are not acted upon by trypsin, while the albumins of a living cancer are. Conversely, cancer cells produce a ferment, malignin, which is inert towards their own dextro-albumins, but can destroy the lævo-albumins of the body.

Injections of trypsin into the body of a patient with cancer should therefore destroy the cancerous cells without harming the normal tissues. Amylopsin should be used in addition, because it is capable of destroying further the cells killed by the trypsin, and thus preventing the toxic effect these dead cells would otherwise produce.

I believe this to be a fair statement in brief of Beard's argument for the use of pancreatic ferments in the treatment of cancer. There are certain criticisms on the theoretical side which I should like to offer at the outset.

Morphologists do not appear to accept Beard's views on the alternation of generations and the invasion of the embryo by the trophoblast; but let that pass. If the rest of the case can be made good, it would afford strong support to his morphological conceptions.

If the death of the embryo and the consequent loss of its pancreatic ferments is the cause of the chorionic cells assuming a malignant activity, what is the maternal pancreas doing during this time? The chorionic villi are deeply inserted into the maternal tissues, and the amount of trypsin which the mother produces must far exceed the secretion possible to the embryo. If pancreatic ferments are antagonistic to malignant disease, patients with advanced pancreatitis should be specially liable to cancer. Malignant disease ought to be preceded by a stage in which signs of pancreatic inadequacy are present; alimentary glycosuria should be common in malignant disease. But none of these conditions are frequently associated.

It might be argued, perhaps, that as it is trypsin, and not trypsinogen, that is responsible, and as the former does not occur till the intestine is reached, malignant disease depends on intestinal conditions rather than on pancreatic lesions. This implies that we are dependent on the reabsorption of trypsin for immunity from cancer. But it is quite an assumption that trypsin is reabsorbed from the bowel, and the view that in cancerous patients it is not so reabsorbed because it has been destroyed by intestinal putrefaction is only an additional assumption.

The statement that living tissues are not digested by trypsin cannot be accepted as generally true. Pawlow found it difficult in his dogs with a pancreatic fistula to prevent the juice from digesting the dog's

own tissues in the neighbourhood. Starling found auto-digestion of the alimentary canal after secretin injections.

Guleke found that a transplanted pancreas digested the surrounding tissues. Indeed, the body would hardly have evolved so many safeguards against tryptic action if trypsin were a harmless substance to its own tissues.

Failure of trypsin injections to produce the same effect must be due either to inactivity of the solution used or to the development of an antitrypsin. As to the former alternative, we have seen that trypsin is a very unstable substance, and in the absence of any material on which to act, rapidly destroys itself. As to the latter, the formation of an antitrypsin has been observed by several authorities (see Cathcart, *Journal of Physiology*, vol. xxxi., p. 497), and it is impossible to dispose of all these by stating, as a supporter of Beard has done, that this only occurs when the pancreas is somewhat decomposed. Of course, it is essential to Beard's hypothesis that trypsin should be an exception to the general rule that injection of ferments causes the production of antiferments. Unfortunately for the hypothesis, the weight of the evidence goes to show that trypsin is no exception; indeed, considering its great digestive power, it is difficult to believe that the body could do without an antitrypsin.

And now for the supposed antithesis between the stereo-chemical structure of normal and trophoblastic

or cancerous tissues. As trypsin is admitted to be capable of digesting all proteins when dead, are we to suppose that lævo-proteins become dextrorotatory in the act of dying? If not, what is the point of the antithesis? Ferments act on bodies of similar molecular configuration, and do not distinguish between living and dead tissues; if they did, animals that swallow their prey alive would have to starve. It is not the ferment that distinguishes between life and death; it is the living tissue that has the power of protecting itself against the ferment.

It is a total fallacy that the body is unable to assimilate food-stuffs of opposite chemical configuration to its own tissues. When we eat cane-sugar it is split up into dextrose and lævulose before it is absorbed, and we can utilize both. On Beard's hypothesis, one of two things must happen every time we take cane-sugar: either the lævorotatory sugar must pass out in the urine, or it must nourish the potential cancer cells in our tissues. As the former does not occur unless an excessive amount is taken, we should, in accepting Beard's view, be forced to the extraordinary conclusion that half the nourishment in every lump of sugar is devoted to developing cancer in our body.

Starting, then, from a morphological conception which is not accepted, he proceeds to a chemical assumption which will not stand examination. On this unstable foundation are reared airy hypotheses

which are opposed to the whole trend of physiological experiment.

All this, of course, is no argument against using injections of trypsin for cancer if empirically they can be shown to be beneficial. But we should be forced to the conclusion that the treatment was effectual on quite other grounds than those for which it was advocated by Beard. And it is not surprising if the beneficial results that have been reported so far are more in accord with general physiological principles than with Beard's views. Thus, Aleindor (*Brit. Med. Journ.*, 1908, vol. i., p. 79) found that injections of trypsin produced digestion of the body proteins, and that a lowered vitality resulted, which in one case he held responsible for metastatic growths at the site of injection. On the other hand, topical application diminished the growths, which is contrary to Beard's conclusions. Amylopsin he found to be no good, either locally or generally. Graves (*Boston Medical and Surgical Journal*, January 23, 1908) states that the only apparent effects he has been able to produce have been by direct injection into the mass. By this means he has been able to produce cessation of growth in a recurrent nodule permanently, and has relieved pain and fœtor in an ulcerated growth, but there was no delay in the onward progress of the disease.

S. and G. F. Keith, after extensively employing the treatment for a year, came to the conclusion that it

was not only useless, but even dangerous. Nephritis has also been reported as a result of trypsin injections, so that altogether it is to be feared that trypsin will take its place in the limbo of many other well-advertised 'cancer cures.'

CHAPTER IV

URIC ACID AND THE PURIN BODIES

It is necessary to form an opinion as to the part that uric acid and allied substances play in disease, and we can only do so by studying their normal behaviour in the body. Uric acid is a subject which has a peculiar fascination for the lay mind, and our patients often seek or wish to impart information upon the point. Again, there is something about uric acid, as there is about alcohol, which seems to turn the mildest-mannered man into a heated partisan. The widest differences of opinion prevail; thus Haig seems to regard it as the cause of nearly all the ills that human flesh is heir to, while Luff regards it as a harmless by-product of metabolism. Between these two views there is plenty of room for the exercise of private judgment.

What are Purin Bodies?—Fischer gave the general name of purins to bodies containing the nucleus C_5N_4 , which will yield two urea molecules on oxidation. Only twelve different purins are known to exist in

124 PHYSIOLOGICAL PRINCIPLES

Nature, though 146 have been prepared in the laboratory. The most important ones are—

Oxy-purins	Hypoxanthin	...	$C_5N_4H_4O$
	Xanthin	...	$C_5N_4H_4O_2$
	Uric acid	...	$C_5N_4H_4O_3$
Amino-purins	Adenin	...	$C_5N_4H_4NH_2$
	Guanin	...	$C_5N_4H_4O.NH_2$
Methyl-purins	Theobromine	...	$C_5N_4H_2(CH_3)_2O_2$
	Caffein and thein	...	$C_5N_4H(CH_3)_3O_2$

The source of urinary purins may be classified thus:

1. *Exogenous purins* from the food. We take these substances in, as—

(a) Methyl-purins in tea, coffee, and cocoa.

(b) Free purins, such as xanthin and hypoxanthin, in meat-extracts.

(c) Bound purins. Nuclei yield purins in their decomposition. The more cells a food contains the more nuclei it has, and therefore the more purins it yields; therefore cellular organs, such as liver and sweetbread, are a great source of purin intake.

2. *Endogenous Purins*.—Even on a purin-free diet the urine contains purin bodies, so that some must come from the body tissues. Their source seems to be the nuclei of breaking-down cells and the muscles.

They cannot come from the nucleo-proteins alone, for Garratt has shown that in fevers the increased uric acid output is not accompanied by an increase in the excretion of phosphates. Phosphoric acid is a constant constituent of nucleo-protein.

About 0·2 gramme of nitrogen is excreted in this form daily. The amount seems to be constant for the same person, provided he be living under constant physiological conditions.

In the following table, taken from Walker Hall, the bound and free purins are estimated together, the foods having been weighed just as they are used in the household :

					Purins in Grains per Pound.
<i>Fish :</i>					
Cod	4·07
Salmon	8·15
<i>Meat :</i>					
Mutton	6·75
Beef	7·96 to 14·45
Chicken	9·06
Liver	19·26
Sweetbread	70·43
Eggs and cheese	almost 0
<i>Vegetables :</i>					
White bread, rice, cabbage, cauliflower, lettuce	0
Potatoes	0·14
Asparagus	1·5
Peas	2·54
Oatmeal	3·46
Beans	4·16
					Purins in Grains per Pint.
<i>Beverages :</i>					
Wines	0
Milk	0·0014
Beer	1·09 to 1·27
					Methyl-purins. Grains per Teacup.
Tea, China	0·075
Tea, Ceylon	1·21
Coffee	1·7

It will be seen from this table that the practice of distinguishing between red and white meats in dieting a gouty patient apparently is unsound if it is regarded as a method of regulating his purin intake. To cut a patient off mutton and give him chicken and sweetbread hardly achieves the object that is presumably in view.

Adler claims, however, that white meats lose their extractives more readily on cooking than do red; thus, veal loses four-fifths of its extractives, while beef loses hardly any. Incidentally, the result of this must be that veal broth is laden with purins.

The Effect of Ingestion of Purin Bodies.—‘If we believe popular medical, to say nothing of lay, opinion, uric acid is a virulent, all-pervading poison,’ says W. G. Smith, ‘yet it is a normal constituent of our bodies, and . . . is regularly found in the blood of birds.’ Now, as Gore points out, ‘uric acid can be no exception to the general law that a substance acts as a poison in direct proportion to the amount of it present in the circulating fluid.’ We know that in leukæmia as much as 5 grammes of uric acid may be excreted in a day from the nuclei of breaking-down leucocytes. If uric acid is a direct poison, why does it not produce symptoms in leukæmia similar to those of ‘uric acid diseases’?

Walker Hall concludes that, although purins have not the powerful toxic properties usually ascribed to them, they are not entirely harmless. He tried the effect of taking considerable amounts while fasting,

with the following results: 1 gramme of *cafein* caused a sensation of warmth in the abdomen and over the whole surface of the body. There was intense headache and some muscular twitching. On a second occasion a similar dose caused fulness in the head, a loss of muscular sense, and confusion of ideas. Half a gramme of *hypoxanthin* caused a slight fulness in the head, and a feeling of stiffness over the whole body. With *uric acid* a dose of $\frac{1}{2}$ gramme caused distinct headache and confused ideas, with a sensation of warmth in the abdomen. On the second occasion the same dose caused slight headache, with sensory disturbances in the abdomen. On the third occasion a dose of 1 gramme caused no symptoms at all. Note, then, the rapid establishment of tolerance, and that the hypoxanthin caused more definite symptoms than the more oxidized uric acid. Repeated injections of hypoxanthin into rabbits caused a distinct cellular reaction in the liver and kidneys, and a significant slowness of growth of the animal. He could not detect any rise of vascular tension.

History of Purins after Ingestion into the Body.—After excision of the kidneys in dogs no uric acid or other purins could be found in the blood even if a diet were given which was rich in purins. This in itself seems fatal to the hypothesis of 'retention' of uric acid, to which so many diseases have been referred. Evidently something in the body destroys purins. It is found that liver extracts will destroy uric acid *in vitro*, while kidney extracts will not. This

power of destruction seems to depend mainly on a ferment, though Austen thinks it is difficult to distinguish between this and the destructive influence of alkalies, which must be present in such an extract. However, Stookey has noted a distinct increase in uricolysis in the body after subcutaneous injection of liver extract.

How does it happen that any purin bodies are excreted in the urine when there is such an active destruction of them going on in the liver? It is due to their escape by the kidneys before destruction can occur. This accords very well with the observation that the increased purin excretion begins even in the first hour after food.

After giving hypoxanthin by mouth the whole of the expected increased output occurs within four hours. If uric acid be given, the whole of the expected output occurs within eight hours. If bound purins—*i.e.*, nucleins—be given, the increased excretion is spread over two or more days. The slowness of their excretion emphasizes the greater metabolic effort they involve, and suggests the contraindication of cellular foods, such as liver and sweetbread, in all conditions of defective metabolism.

About half of the injected uric acid, or ingested xanthin or hypoxanthin, and about a quarter of the nuclear purins, appear in the urine as uric acid, while one-third of the caffeine or the theobromine reappears in the urine as xanthin or hypoxanthin, the rest being destroyed in the liver, giving rise to

urea. Note, as another point against the retention hypothesis, that the readily soluble hypoxanthin reappears in the urine to just the same extent as uric acid, which is so sparingly soluble.

Significance of Increased Purin Excretion.—We know that the daily manufacture of purins from the bodily tissues amounts to 0·2 gramme of nitrogen. This should be the amount excreted on a purin-free diet. On a mixed diet it will be higher, different authorities giving 0·3 to 0·45 gramme of purin nitrogen as ordinary figures. If it is higher than this, two alternatives present themselves: (a) There is an excessive purin intake, or (b) there is defective action of the liver, which is failing to break down the purins in the way it should.

In either alternative the diet should be revised.

Estimation of the Urinary Purins.—The only method suitable for clinical work is Walker Hall's purinometer. The apparatus consists of an upright tube, divided by a stopcock into a larger upper graduated portion and a smaller lower reservoir of known cubical capacity. The tap being turned off, urine is poured in up to 90 c.c.; then the tap is turned on, and 20 c.c. of the following solution added:

Ludwig's magnesium mixture	100 c.c.
Ammonia solution 20 per cent.	100 c.c.
Talc	10 grammes.

When the precipitated phosphates have settled in the reservoir (which should not take more than ten

130 PHYSIOLOGICAL PRINCIPLES

to fifteen minutes), the tap is turned off again. To the clear fluid in the upper part of the tube 18 c.c. of this second solution are added :

Silver nitrate	1 gramme.
Ammonia (strong)	100 c.c.
Talc	5 grammes.
Distilled water	100 c.c.

The urinary purins come down as a granular yellowish precipitate. Any silver chloride should be re-dissolved by the ammonia, but it may be necessary to add a little more ammonia should it persist as a pure white precipitate. The tube must be vigorously shaken for a minute to break up the precipitate. It is then allowed to stand in the dark for twenty-four hours, when the number of c.c. of precipitate is read off. A table supplied with the apparatus gives the amount of purin nitrogen to which this corresponds. If the total amount of urine is known, the total purin output can be easily calculated.

As with all sedimentation methods, the specific gravity should be fairly constant, 1015 being about the point at which the results are most constant. The urine should therefore be diluted or concentrated by evaporation as required. Albumen, if present, should be removed by boiling and filtering. It is best not to allow the precipitate to settle in the apparatus, but to pour it off into an ordinary c.c. measure, because the constriction in the tube near

the tap is a great drawback to accurate sedimentation. This has the additional advantage that another estimation can be proceeded with the same day. The results come out rather lower than with Haycraft's method, but this does not matter in making a series of comparative observations, for which purpose alone it is suitable. The process is simple, and takes but little time to start, while the reading off next day can be done at a glance.*

Though, in order to know exactly what is going on, we ought to calculate the amount of purins in the diet taken so as to see whether they are being duly metabolized, still, we can come to some conclusions if the purinometer gives us a high reading on an ordinary mixed diet. The liver is not doing its work properly. Uratic deposit becomes then a symptom, and not the cause of disease. It is merely an indication of hepatic insufficiency. Thus in *gout* we find that food purins are badly metabolized. In *cirrhosis of the liver* the destruction of the liver cells results in their being unable to break down the purins as they should.

We must enlarge our conception of the work that the liver has to do. It not only forms urea, but it does so, in part at least, by destroying uric acid and allied bodies; this it does apparently by

* Messrs. Gallenkamp supply the apparatus for 25s. Their charge for the solution is 5s. for about 200 c.c., which works out at about sixpence an analysis. Any dispenser, however, can prepare the solutions without difficulty, and the cost of the materials is trifling.

a number of specific ferments; and we may perhaps look forward to the day when, as Hopkins says, we shall not speak of a patient possessing a diathesis, but of his lacking some one of these ferments. It is only reasonable treatment in such cases to diminish the intake of substances which are not necessary as foods, and which tax the liver to metabolize them and the kidney to excrete them.

I believe we may look upon a person who is readily poisoned by purins in the same light as the person who has cystinuria, alkaptonuria, or pentosuria—*i.e.*, they all lack a link in the chain of protein katabolism, so that intermediate products appear in the urine instead of the usual end-products. The most curious point, to my mind, about the man who cannot metabolize purins is his fixed belief that the rest of mankind suffers from a similar incapacity.

This modified conception of the source and history of purin bodies should diminish our ardour in trying to wash uric acid out of the system. 'Much therapy is directed against this necessary result of nuclein metabolism,' but, as a matter of fact, most drugs have an insignificant effect in increasing the elimination of uric acid and its allies.

Water, by producing diuresis, certainly increases the output. It seems to me chemically impossible that *lithium salts* can have any effect in this direction. We know that chemical action is determined both by the mass and the avidity of the various interacting bodies, but also that if in any mixture of

acids and bases an insoluble salt can be formed, it will be formed. In face of this, what can be the use of a few grains of lithia introduced into the body to combat an amount of sodium which, in addition to all the advantage of mass reaction, forms the less soluble salt? Lithium is, moreover, distinctly depressing in its action on the spinal cord, motor nerves, and alimentary canal. I have seen a patient who had certainly done himself harm by taking large quantities of lithia in order to dissolve out the uric acid by which he imagined himself to be obsessed.

Piperazin has been shown by Fawcett and Gordon to have no solvent action even in full doses. *Urotropin* can cause a very slight increase in the purin output.

Salicylates, on the other hand, can cause a very markedly increased output—sometimes as much as 50 per cent. But it is not a little disturbing to find that this increase will occur even on a purin-free diet. There are three possible explanations:

1. That salicylate washes out retained uric acid. But since the liver rapidly destroys uric acid, retention does not occur, and therefore washing out cannot be effected.
2. That the drug causes increased katabolism of the tissues. But the increase is too great, and no marked loss of weight occurs on administration of salicylates such as this hypothesis would necessitate.
3. That it causes synthetic production of purins.

This is not proven, but by a process of exclusion seems the only possible explanation. It would appear ironical if, in their enthusiasm for 'washing out' uric acid, those to whom it is anathema are merely increasing its production.

The action of *alcohol* is complicated. With malt liquors there is an actual intake of purins, while in all cases alcohol leads to diminished solubility of purins.

Minkowski has suggested that *thyminic acid* (an organic acid containing phosphorus) is the substance which holds uric acid in solution in the circulation. Quadriurate of soda has for some time been regarded merely as a mixture. Thyminic acid can hold its own weight of uric acid in solution at 20° C., and 50 per cent. more at body temperature. I was therefore very anxious to test whether it would prevent uratic deposition, but application to several large firms was in vain; I could not obtain the drug. However, Fenner was more fortunate. He obtained and employed it in doses of 4 to 8 grammes three times a day, with the following results (*Lancet*, July 1, 1905):

'During its exhibition I have presented no other drug, and the results have been most gratifying. In acute cases it quickly cuts short the inflammatory condition, and leads to rapid convalescence; in chronic cases prolonged administration of the drug has led to marked improvement in nearly every case. I have been particularly pleased with the result of

treatment in cases of gouty glycosuria, gravel, gouty eczema, and obesity.'

Although we no longer believe that deposit of biurate of soda explains the whole pathology of gout, and look upon it rather as a symptom, yet we can quite understand that a case of gout would be improved if the deposit could be prevented. It is therefore reasonable to try this drug, which is apparently free from injurious properties; but I am bound to add that our experience with it at the Metropolitan Hospital has not been so gratifying as Fenner's.

Prevention of Deposition of Uric Acid in Urine.—Though we can do so little, and perhaps should do little, to increase the output of uric acid, we can and ought to check its deposit in the crystalline state in the urine, causing symptoms of stone and gravel. Sir William Roberts showed the importance of high acidity and high percentage in causing this deposit.

Acidity is at its height during the fasting hours and seldom is a marked feature during digestion, owing to the loss of acid by the gastric juice. It is usually sufficient to give 20 grammes of potassium citrate night and morning to correct high acidity. There is, however, one precaution which I have not seen mentioned, but which seems to me very important. If uric acid deposit has already occurred in the form of a calculus, rendering the urine alkaline will cause growth of the calculus by accretion of phos-

phates. I therefore tell such patients to put a piece of red litmus-paper into the morning urine. If it turns blue, the drug must be diminished in amount until this just does not occur. Fresh fruit, such as pears, green figs, dates, oranges, and grapes, have been shown by Smith Jerome to have a similar action in checking high acidity.

High percentage of uric acid may be absolute or relative—that is, the total output may be increased or the urine may be concentrated. Both may favour deposition. The former should be regulated by cutting off foods rich in purins, the latter by diluting the urine. Patients do not seem to care to be ordered to drink plain water. Potash water is preferable to soda water, because of the relative insolubility of the sodium salts. But, for the reasons I gave when considering the action of lithia, it is the water which is the chief therapeutic agent. Gee has pointed out the extraordinary effect of *whey* in preventing uric acid deposits, and I have repeatedly confirmed this. I do not know whether the effect is due to its action as a diuretic, but there is no doubt as to the fact. A breakfastcupful should be given twice or thrice a day.

To summarize briefly the conclusions reached in this chapter :

1. Uric acid is merely one, and one of the less toxic purin bodies.
2. Purins in the urine come partly from exogenous

sources (free and bound purins of food), and partly from endogenous sources (nucleins and muscle).

3. Though administration of doses of $\frac{1}{2}$ to 1 gramme may produce mildly toxic symptoms, tolerance is soon established. In some animals repeated doses may produce a cumulative effect.

4. Purins are destroyed to about 50 per cent. under normal conditions in the liver. If their excretion be delayed, a larger amount is destroyed.

5. Abnormally high purin excretion means either an abnormal ingestion or defective action on the part of the liver—*i.e.*, it is symptomatic rather than the essential feature of certain diseases. It may result from the excessive breaking down of nuclei. Thus it is largely excreted in leukæmia because of the excessive number of leucocytes, yet it produces no symptoms.

6. The purinometer affords a convenient method of estimating urinary purins. By it we can readily check the effect of diet. A high purin excretion, say above 0.3 gramme of nitrogen, would suggest a revision of the diet, rather to avoid overtaxing the liver than because of any specific toxic action.

7. Many drugs have been employed to increase the purin excretion under a misapprehension of the significance of purins, and are mostly inadequate for the purpose. The salicylates are effective, but as they act on the endogenous purins they are of doubtful expediency. There is a rational basis for the use of

thyminic acid (solurol), but it is still in the experimental stage.

8. The deposition of uric acid in the urine, on the other hand, is more readily controlled by diminishing its acidity and the degree of concentration.

CHAPTER V

OXALURIA, PHOSPHATURIA, AND ALBUMINURIA

OXALATE crystals, phosphatic deposits, and albumen may each occur in the urine under varying conditions, in which they may have a widely different significance. Physiological considerations may help us to rightly appraise these, and point to a line of rational treatment.

Oxaluria.

The urine contains substances which have been introduced with the food (exogenous) and substances which have been formed within the body (endogenous).

The origin of oxalates from the food is clear ; their formation within the body is not easily proved.

Small quantities of oxalates are normally present, but the only form in which they have any clinical significance is when they are deposited as calcium oxalate in envelope, or, less commonly, dumb-bell crystals.

Sources of Urinary Oxalates—(a) *Direct Ingestion of Oxalates in the Food*.—Rhubarb, spinach, straw-

berries, and tomatoes are the articles which, in my experience, are most prone to produce oxaluria in sufficient amount to cause symptoms. But many other articles of diet contain oxalates—*e.g.*, figs, potatoes, beetroot, French beans, plums, tea, coffee, and cocoa.

On the other hand, the following articles contain little or no oxalates: peas, asparagus, mushrooms, onions, lettuce, rice, cauliflower, pears, peaches, grapes, melons, wheat, and oats.

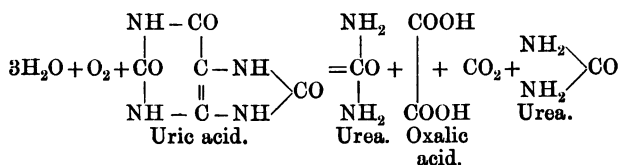
Baldwin's *oxalate-free diet* is composed of meat, milk, eggs, sugar, butter, wheat-meal, rice, and biscuits.

The acidity of the gastric contents seems to influence the absorption of these alimentary oxalates. Thus, if there is no hydrochloric acid in the gastric juice, there may be no oxalates in the urine, even if spinach is given as food; but on giving hydrochloric acid by the mouth oxalates will appear. Similarly, we may reduce these alimentary oxalates by giving alkalies.

(b) *From Gastric Fermentation.*—It is curious that oxalates will appear under precisely opposite conditions—when there is no hydrochloric acid. But to produce them then, abundant fermentation must be going on, and sugar must be present, giving rise to oxalic acid by its fermentation. In this process, as the oxalates are formed in the gastric contents, it really amounts here, again, to ingestion as the source of the oxaluria. Thus Baldwin produced oxaluria in dogs by feeding on meat and excess of dextrose. A

mucous gastritis with absence of free hydrochloric acid resulted, and oxalic acid was found in the gastric contents.

(c) *Endogenous Formation*.—It is tempting to look upon uric acid as a source of oxalates in urine. This view has been widely held. In the laboratory decomposition of uric acid results in the formation of oxalic acid.



In the body a good deal of the uric acid is decomposed in the liver. If uric acid is added to an excised liver, oxalic acid is formed. If the metabolism of the liver is incomplete, it is easy to suppose the central carbon chain of the uric acid is not completely oxidized, when oxaluria would result.

Several observers (Dunlop, Baldwin, Rendle Short), however, have been unable to find any oxalates in the urine on a milk diet, while others have found traces. We may conclude that endogenous formation does not occur in sufficient quantity to produce symptoms. This clears the ground and enables us to assert that symptoms of oxaluria are the result either of ingestion of food rich in oxalates or of fermentative dyspepsia, especially with excess of carbohydrate diet.

Symptoms—(a) *Urinary Irritation*.—Most of the

cases only show this. Everyone is probably familiar with the outbreak of these cases in the strawberry season, especially if the weather be very hot, so that the urine is also very concentrated. I would suggest that there are several factors at work here. Strawberries contain oxalates, cream tends to dyspepsia, and the sugar by its fermentation produces more oxalates.

Micturition becomes painful, and is followed by prolonged smarting. Hæmaturia is not infrequent. Envelope crystals are found abundantly in the urine. The association with intermittent albuminuria I will discuss later. I know men in whom such symptoms occur every summer, and one man in whom they occur every time he eats rhubarb.

(b) *Oxalate calculi* may form; they are hard mulberry-stones, usually mixed with uric acid.

(c) *Remoter Symptoms*.—It follows, from what I have said, that fermentative dyspepsia will lead to oxaluria. The so-called 'remoter symptoms' and the oxaluria must be referred to a common cause. We must not regard the oxaluria as causing them.

Such symptoms often occur in crises. These crises are sometimes precipitated by worry or overwork, sometimes by some intercurrent disorder. They consist of attacks of depression and lassitude, headache, smarting pains on micturition, neuralgic pains in the back, chiefly referred to the kidney. The patient often becomes hypochondriacal. This oxaluria is the index of a very low state of health (Gee). As an example I may quote the following case :

A nervous, delicate, hard-working youth consulted me for paroxysms of pain in the left side; nothing could be made out on physical examination, and a skiagram revealed nothing. The urine contained abundant crystals of calcium oxalate, but no albumen. The paroxysms generally came on if he overworked or took much muscular exertion; they left him fatigued and much depressed. Subsequently he had two attacks of hæmaturia, the second rather severe, and accompanied by much pain. A stone was suspected, and his kidney was explored, but nothing was found to account for the symptoms. The patient still has occasional attacks of pain, but has had no more hæmaturia.

Treatment of Oxaluria.—The recognised treatment is to order abstention from oxalate-containing foods and to administer magnesia, since the oxalates are more soluble in the presence of magnesia. Peas should be taken when in season, as they are poor in oxalates and rich in magnesia. We must remember that although the amount of oxalate deposited is no guide to the total oxalate excreted, it is only the deposit which causes the urinary symptoms.

The avoidance of so many things which are particularly pleasant in hot weather is an irksome prescription, and if anything can be done to mitigate the hardship it should be done.

Potassium citrate may help us; it probably acts in two ways at least:

1. As a diuretic it dilutes the urine.

2. By combining with the calcium it prevents the formation of calcium oxalate crystals. Martin showed that citrates threw calcium out of action by forming a soluble double salt. It is well known that citrates prevent the curdling of milk and the clotting of blood for this reason, and they have therefore been extensively used in the treatment of gastro-intestinal conditions and phlebitis, and, I think, successfully.

I have employed them in 'direct' oxaluria with success also. Some observers prefer to employ lemon-juice to sodium or potassium citrate, and claim that in phlebitis, at any rate, it is much more effective. Now, if we can tell our patients that they need not give up strawberries altogether if they will also drink lemon squash, I do not think they have any cause for complaint, and, seriously, I believe we shall effect the desired object. A caution against much sugar while on this treatment should also be given.

In the nervous cases we must treat the digestive disturbance also, and direct our attention to preventing fermentation of the sugar. They generally require a holiday and change of air.

Phosphaturia.

Normally phosphates are present in the urine as—

(a) Acid phosphates of sodium and potassium.

(b) Earthy phosphates of calcium and magnesium.

It is only the latter that can form a deposit. Such deposit may occur—

1. In the bladder, so that the last portion of the urine is milky. This is often mistaken for spermatorrhœa; the patient becomes needlessly depressed, and falls an easy prey to quacks.

2. As an iridescent pellicle on the surface of the urine when it has been passed.

3. Only on boiling the urine, when acidification is necessary to prevent confusing it with albumen.

Calcium phosphate forms a deposit of stellar crystals, magnesium phosphate appears as rectangular plates with bevelled edges, while ammonio-magnesium phosphate ('triple phosphate') forms 'knife-rest' or 'coffin-lid' crystals.

The term 'phosphaturia' is somewhat loosely applied to any condition in which these various deposits occur. But it is clear that such deposit does not necessarily mean any increase in the total output of phosphates, since under no circumstances will the sodium and potassium phosphates be precipitated, while the earthy phosphates will be deposited on adding any alkali to any urine. Quantitative estimation would be necessary to prove an increase.

Usually phosphaturia is merely a sign of diminished acidity of the urine.*

Now, if there is excessive secretion of hydrochloric acid in the gastric juice, there will be less acid at the

* Joulie lays great stress on the ratio of total phosphates to total acidity. I have not dealt with his views as to the significance of alterations in that ratio, as his premises are not proved as yet.

disposal of the urine. Phosphaturia is therefore very common in hyperchlorhydria, and I always look for it to confirm my diagnosis of this condition.

Again, if there be cystitis, the ammoniacal decomposition will lead to a deposit of phosphates which will take the form of crystals of 'triple phosphates.' The occurrence of 'knife-rest' crystals at once suggests cystitis. Recently I saw a case where the passage of these crystals had occurred with hæmaturia at intervals for over a year. Between the attacks the urine was quite normal; but a stone was ultimately found.

There is, however, a residue of cases where the output is really increased from the normal $2\frac{1}{2}$ grammes of phosphoric acid to perhaps 7 or 9 grammes. Here the earthy phosphates will probably be in excess. The ratio of earthy to alkaline phosphates, which is normally 1 to 2, may rise to 5 to 2. It was formerly thought that this was due to excessive breaking-down of the phosphates of the brain, especially as it is common in neurasthenia, but there is no proof of this.

It must be remembered that wasting must cause an increased excretion of phosphates, because the disintegration of nucleo-proteids yields phosphates. Conversely, phosphates are diminished in the urine in pregnancy and in convalescence after fevers, because they are required for building up. Phosphaturia may, therefore, be merely a symptom of wasting. Sometimes no definite cause for the wasting can be found. Thus the editor of a 'hustling' journal,

æt. thirty-eight years, consulted me for loss of weight (28 pounds in two months). He was suffering from depression and 'brain-fag,' but there was nothing objective except phosphaturia. Tonics and alteration in his mode of life led to great improvement. Again, a man, æt. fifty-two years, was sent to me to find a cause of his loss of flesh. He had formerly been in a business which had declined so much that he had recently taken up a new occupation which entailed much walking. Some swelling of the legs came on, and he became very thin. Except some old adhesions round his shoulder-joint, which explained the pain and limitation of movement he experienced there, I could find nothing beyond phosphaturia. As he gradually became accustomed to his new occupation, he put on flesh again under ordinary tonic treatment.

Sometimes the cause of the wasting is definite. Thus, recently I reported an instance of multiple myeloid tumours leading to albumosuria (*British Medical Journal*, September 14, 1907). Here there was marked phosphaturia, no doubt in consequence of the earthy salts being set free by the destruction of the bones.

Phosphaturia may also occur in cases of marked depression without wasting. It was the only objective sign I could find in a young man who had recently gone into business on his own account, and who consulted me for paroxysms of fear of failure. It was present also in the case of a young man of the anxious, nervous type, who was on the Stock

Exchange, and consulted me for headache, insomnia, and impairment of memory.

Probably the phosphaturia in these cases is symptomatic of a diminished formation of acid due to a general depression of metabolism.

In Ralfe's opinion cases of phosphaturia with wasting are apt to go on to serious organic diseases if they do not rapidly yield to treatment, but I have only observed such a sequence once. A man, aged fifty years, had much anxiety on account of the prolonged and ultimately fatal illness of his wife. He was much frightened because his urine had an iridescent scum on it. I found it was composed of phosphates, the urine being scarcely acid. Two or three years later he developed chronic interstitial nephritis, and had an attack of cerebral hæmorrhage which left him aphasic. I do not think, however, that there was any connection between the phosphaturia and this event. More probably the prolonged anxiety caused both depressed metabolism and high tension.

Treatment.—We must remember that phosphaturia is a symptom and not a disease.

1. If triple phosphates are present, seek a cause for cystitis and treat that.
 2. If phosphaturia depends on hyperchlorhydria, the digestive condition requires treatment.
 3. If it is associated with wasting, it is the cause of the wasting that calls for attention.
 4. If it is a symptom of depressed metabolism, give the patient the acid he cannot make, prefer-
-

ably combined with tonics, and he is usually much benefited.

Now, phosphoric acid usually suits them well. If their symptoms were really due to phosphatic loss, I should hardly expect that to be the case, because there would already be excess of circulating phosphate, and I cannot see how the tissues can discriminate between this and the administered phosphate. Moreover, if a fish diet be given, rich in phosphates but not acid, the phosphaturia will probably be aggravated. Therefore it is simply because it is acid that phosphoric acid does good, and in my experience it does not matter whether you give phosphoric or nitro-hydrochloric acid. But we should give inorganic acids, and with them tincture of *nux vomica*.

It is an interesting point of contrast that neurasthenics tend to oxaluria with very acid urine, but to phosphaturia if the urine is not very acid.

Albuminuria.

We may classify the causes of true or renal albuminuria as follows (Tirard):

1. Without definite structural change of renal tissue:

- (a) Mechanical—*e.g.*, from failing heart.
- (b) Hæmatogenous—*e.g.*, in the anæmias and in fevers.
- (c) 'Functional.'

2. With definite structural change of renal tissue.

'*Functional*' *albuminuria* has also been called alimentary, postural, cyclic, adolescent, to mention only a few of the names which have been given to it. Alimentary albuminuria is extremely difficult to produce. Certain experiments by D'Arcy Power upon himself are usually quoted as evidence of its existence. It is true that albumen appeared in his urine on the first day of the experiment, after twelve eggs had been eaten, but it disappeared in the evening, and did not reappear till the afternoon of the third day, after the consumption of forty-eight eggs. It was found again during the evening of this day, after which it disappeared again, and had not reappeared at the end of the experiment, by which time sixty-five eggs had been taken. Only once was the albumen present in sufficient amount to enable its coagulation, point to be determined. It will be noted that there is very little connection between the number of eggs consumed and the amount of albumen. A very significant point, which seems to have escaped notice, is that at this time D'Arcy Power was aged twenty-two, and that the occurrence of the albuminuria was always observed after a considerable amount of exercise had been taken. Now, transient albuminuria after severe exercise is common in young men, as we shall see, without excess of albuminous diet.

'*Functional*' albuminuria is not an uncommon

condition in males between puberty and marriage. Dukes found it in 16 per cent. of all the boys entering Rugby School at the ages of thirteen or fourteen. The strain of examinations seems to be a factor. A young man I knew who was working for an examination in physiology happened to test his urine. To his alarm, it was loaded with albumen. He took a holiday, and the urine soon became free from albumen. Some years later the albumen returned during an intercurrent illness, again disappearing when he recovered from it. He is now a healthy man in busy practice.

The subjects of this condition are usually anæmic, weedy youths with a dull, heavy aspect, and a tendency to fainting. Dukes says that boys who faint in chapel are almost certain to be albuminurics. Their hearts are often excitable, and the youths vaguely diagnosed as 'weak hearts' are often examples of this condition.

Dukes divides them into three classes :

1. By far the largest class exhibited an increased arterial tension in consequence of irritability of the vasomotor nerves. The tension is, however, so unstable that it varies from hour to hour and day to day. This he regards as pathognomonic of the disease.

2. The next most extensive class comprises those who have cold, clammy, congested extremities, accompanied by a large, feeble, compressible pulse arising from deficient vasomotor control.

3. The remainder are the spare, highly-strung, oversensitive neurotics.

But albuminuria may occur after violent exercise in almost any young adult, even though not corresponding with any of these types. Collier found albumen present in the urine of every one of the Oxford crew of 1906 after rowing a course. In the case of half of them the amount of albumen was quite large, and in men who went in for running races the albuminuria was even more pronounced. In all these cases he found the urine passed in the early morning to be free from albumen.

Cold bathing is another factor in inducing transient albuminuria, presumably due to driving of blood from the periphery into the splanchnic area. The protein present is chiefly the serum albumen, to which the kidney is more permeable.

In the cases where albumen readily occurs without some special strain hyaline casts may be seen, and often calcium oxalate crystals. The effect of posture is important. Albumen is absent from the urine passed first thing on rising, because this was secreted while recumbent; but it appears in urine secreted while in the upright position. With the fainting and the variable tension this strongly suggests a vasomotor element. A lax condition of the vasomotor system failing to compensate for the effect of gravity would allow both cerebral anæmia and back pressure on the kidney to occur.

Observations of the blood-pressure confirm this;

whereas change of posture has an insignificant effect on the blood-pressure of a normal person, there may be a difference of 40 millimetres between the pressure in the upright and recumbent position in these patients. I have seen a case in a girl where there was a variation of 35 millimetres.

Edel, in eight cases of this condition, found a fall of pressure under circumstances which ordinarily cause a rise in the healthy man. Coincidentally with this fall, albumen appeared in the urine. Facts such as these place vasomotor insufficiency in an indisputable position as the principal factor in this form of albuminuria, to which the name 'orthostatic' may therefore fairly be applied.

Sir A. E. Wright noted a lessened coagulability of the blood in this condition, which would cause diminished viscosity. Calcium salts reduce the coagulation time and increase the viscosity. He found that calcium salts would control 'functional' albuminuria, whereas organic albuminuria would not be diminished, and might be increased. The subjects of 'functional' albuminuria have often been growing rapidly, so that there is an extra demand for calcium on the part of the tissues. He therefore considered the condition 'hæmatogenous' in origin, and allied to a 'serous exudate' such as occurs in urticaria.

These observations are very important, because, whether we accept this view of the pathology of the condition or not, it provides us with a convenient clinical test for 'functional' albuminuria.

Fifteen grains of calcium lactate three times a day in water should control the albumen in these cases. There is a possible fallacy, because the albumen often spontaneously disappears or is only present at certain times in the day. Systematic observations are required under hospital conditions, and these cases are, of course, commoner in private practice.

In four cases which I believed to be of this character the calcium lactate readily controlled the albumen, whereas in organic albuminuria I found it to have no effect as determined by Esbach's albuminometer.

Hingston Fox employed it in seven cases he thought were functional, and in all the albuminuria ceased, whereas in nine cases apparently organic the albuminuria persisted.

While admitting this hæmatogenous element, we must not overlook the vasomotor element, which I believe to be of much greater importance.

The association of oxaluria and albuminuria has led to some speculation. The view commonly held is that the excretion of the calcium oxalate crystals mechanically irritates the kidney. The fact that actual hæmaturia occurs in the severer cases of oxaluria rather supports this. Berguignan regards both oxaluria and albuminuria as the result of absorption from the bowel by a damaged epithelium. But a damaged epithelium takes up albumen less readily than normal, and, as I shall show presently,

diminished protein diet is not able to diminish albuminuria. I certainly prefer the simpler hypothesis of mechanical irritation.

Prognosis. — Dukes, who has probably had a unique experience of this condition, has totally abandoned his former opinion that it tended to organic kidney disease, for he has found that his patients even thirty years later were robust men. In fact, he has only found albumen subsequently in one of these cases, and that was in a boy who had only recently left school.

The question is one of great importance in connection with life insurance. At present the attitude of the offices towards albuminuria is one of total rejection or of heavy loading. Is this fair? I believe it is justified by some on the ground that the expectation of life is so much lower in albuminurics. Of course it is, if post-scarlatinal nephritis and other organic cases are included. They would naturally bring down the average. But has any attempt been made in such tables to exclude obviously organic cases? I believe not. Now that we have in calcium lactate a simply and readily applied test by which the functional can be discriminated from the organic, it seems to me that the rules of insurance companies and public services should be relaxed. It is not the duty of the medical man who examines for the companies or services to apply the test. Indeed, this would open the door to abuses, for he has no business to treat as patients persons coming before him for

examination. But the general practitioner can fortify his patient against the ordeal of examination by administering calcium lactate, and I can see no objection to his doing so; for he will not be able to secure the acceptance of sufferers from organic nephritis, but only of those who will almost certainly be free from albuminuria when adolescence is past.

Treatment.—Having assured ourselves by controlling the albuminuria by calcium lactate, by excluding the presence of casts other than hyaline, and by noting the effect of posture on the blood-pressure, that the case is one of orthostatic albuminuria, the first step in treatment is to reassure the patient. He usually comes before us, after the shock of rejection or postponement of his proposal for life insurance, believing himself to be the subject of an incurable disease, and is naturally apt to become hypochondriacal. Next a tonic line of treatment and a holiday are indicated, and usually that is all that is needed. I have used digitalis as well to brace up the lax blood-vessels, and so far as I can judge the effect has been good, the general condition (such as the tendency to fainting) improving as well as the albuminuria ceasing.

Organic Albuminuria.—A defective kidney not only lets things pass out which it should retain, it also retains things which it should excrete.

Many of the symptoms are due to the latter factor. Thus, to take a simple example, the failure of the kidney to excrete water and salt is responsible for the

œdema. In Bright's disease we have probably tended to lay too much stress on the albuminuria. In the chronic parenchymatous form no doubt the drain on the albuminous constituents may become serious, and a secondary anæmia results. But such high degrees of albuminuria are uncommon, and I think we are beginning to realize that this one symptom has unduly dominated our conception of the disease. Von Noorden thinks that any wasting is just as much explained by the monotonous diet as by the loss of albumen.

Thus, when we proceed to limit the protein diet rigidly in Bright's disease, are we not led away by false analogies with glycosuria? Whereas there are the following essential differences :

1. The sugar can be replaced by other things in a diet, while the protein cannot.

2. The sugar excretion is preceded by an excess of sugar in the blood; albuminuria is not preceded by excess of albumen in the blood. The latter is due to a kidney lesion, the former is not.

3. Recent work shows that there is a great breaking down of the protein molecule into its constituent groups before it is absorbed into the body. The simple conception of Liebig, according to which the protein food is simply hydrolyzed into peptone, and then assimilated into the tissues with no further change than dehydration, is no longer held.

It has been well said that, just as a Gothic cathedral could not be built out of a classical temple without

reducing it to its constituent stones, so the protein of the tissues cannot be built out of the protein of the food without splitting it up into its simple constituent groups.

Even admitting that Power's experiments prove that it is possible for protein to 'run through' the body, we may say that for all practical purposes this does not occur. For though a nephritic kidney is unduly permeable to albumen, it will not affect the question, because the conclusion would be that the amount of albumen circulating as such is not increased by a protein meal, until such enormous amounts as twelve eggs are taken at one sitting.

I have tested this point several times by estimating the albuminuria on varying diets and comparing it with the urea and total nitrogen excreted.

As an example the following case of parenchymatous nephritis may be taken :

Diet.	Albumen Nitrogen.	Total Nitrogen, less Albumen Nitrogen.
	Gramme.	Grammes.
Milk diet, and one pint beef-tea	0·562	6·17
" " only	0·6	7·46
" " and one egg	0·69	9·77
" " and two eggs	0·7	7·91
" " and three eggs	0·649	7·6

These figures represent the average of several days on the same diet, so as to avoid the disturbance which would be introduced by the diet of one day not being eliminated till the next. From them it can be

seen that the addition of three eggs to the diet did not really affect the albuminuria.

Formerly I used to estimate the ratio $\frac{\text{Urea N}}{\text{Alb. N}}$ on different diets, and if it increased when the protein of the diet was increased, I concluded the increased diet was beneficial, as the patient was metabolizing it. But I think this position is unjustifiable, and I have abandoned it. For consider what happens when we give a normal individual an excess of protein food: he turns it into urea, and excretes it as quickly as possible. The mere fact that the nephritic can turn his protein into urea does not prove he has done any good with that protein. Indeed, evidence is accumulating that such protein excess never gets built up into protoplasm at all.

For this reason it seems to me that the amount of urea secreted in the day gives very little information as to the severity of a case of Bright's disease unless the diet is carefully taken into consideration. Thus a falling urea excretion on a constant diet would have some significance. Of course, a patient on the diet ordinarily given in nephritis passes less urea than normal, because he is given a diet poor in protein. But the output probably will not be so little as that of a healthy fasting man, while it will certainly be more than that of a man on Folin's diet of starch and cream, in which the nitrogenous excretion is reduced to a minimum, because so much of the energy is derived from sources other than protein.

We know now the physiological minimum of protein is much less than the 100 to 125 grammes formerly ordained. Chittenden's experiments on the effect of a reduced protein diet are by now familiar to all. From observations on himself, his assistants, students, and a squad of soldiers, he concluded that weight and nitrogenous equilibrium could be kept up on 50 to 60 grammes protein a day or even less, with no diminution of physical or mental fitness, but rather an increase.

But is the physiological minimum the physiological optimum? as Hutchison pertinently asks. Experience goes to show that where we have, side by side, a race living on a protein-rich diet, and one living on a protein-poor diet, such as the Europeans and natives in India, the incidence of an epidemic and the mortality-rate is much higher in the race that takes little protein. It is noteworthy, too, that the rapid rise of Japan corresponds fairly closely to the adoption of a more liberal nitrogenous diet.

Chittenden's work has, however, proved one fact of great importance—*i.e.*, that of our protein diet very little is used for direct repair of tissue waste. Doubtless much of the rest is used as a source of energy, and it is at least probable that the ammonia groups set free from this protein excess are useful in neutralizing acids that might otherwise lead to acid intoxication.

What is the bearing of all this on the dietetic treatment of chronic nephritis? We may conclude that

too rigid a limitation of the protein diet with the idea of diminishing the albuminuria is bad, because it cannot effect the desired object, and deprives the patient of an essential form of nourishment. On the other hand, an excessive protein diet is inadvisable, even if the patient can metabolize it, because he is getting the energy in a form that throws work on to the damaged excretory organs. What is the happy mean? I would suggest that we can arrive at it theoretically in the following way:

Chittenden's diet gives us the physiological minimum of protein. As the amount of protein in the diet has no appreciable effect on the amount of albumen in the urine, a patient with nephritis would not be able to maintain his nitrogenous equilibrium on Chittenden's diet. We must add to this diet an amount of protein equal to the albumen lost in the urine,* when we shall be giving just enough to maintain equilibrium and yet not be taxing the kidney by calling upon it for any unnecessary work.

We should naturally avoid meat extracts and cellular organs, such as sweetbread, because they contain a large proportion of purins which, though

* A convenient rule is this: when the reading of the albuminometer is 5 and the amount of urine is 2 pints, the patient is excreting as much protein as is contained in one egg. I take these figures because they admit of simple proportional calculation, and also because they represent the amount of albumen excreted in a case of chronic parenchymatous nephritis of average severity—i.e., 6 grammes, which is the amount of protein in one egg.

useless for nutrition, have to be excreted by the kidney. This is contrary to the principle of physiological rest. But we must equally avoid the monotony of diet which leads to failure of appetite and consequent wasting, while it is incapable of affecting the albuminuria. We can safely permit a much greater variety of diet than is allowed on the orthodox lines. For instance, I believe from my analyses that eggs and things made with eggs certainly may be allowed.

It is undesirable to restrict such patients to milk, which is too dilute a form of food for them, and may increase the œdema. Salt should not be allowed, since it is badly eliminated in many cases of nephritis, and, accumulating in the tissues, increases the œdema by raising the osmotic pressure. Indeed, as Bryant found, even a man with healthy heart and kidneys may develop œdema as the result of taking excess of salt. The substitution of butter and lemon-juice will usually satisfy the patient.

In following this plan we shall avoid adding to the miseries of sufferers from an incurable disease by enforcing unnecessary restrictions. If it be desired to guard against the dangers of possible nitrogen retention, Ernberg's plan may be followed of interposing periods of a week or a fortnight during which a diet poor in protein is taken. But prolonged nitrogen starvation is as bad for a nephritic as for anyone else.

The rules which guide us in acute nephritis or in exacerbations of chronic nephritis are somewhat

different, however. 'In acute affections we concentrate our attention on the diseased organ, whilst in chronic cases we keep the general condition of the patient more in view' (von Noorden). Nitrogen retention is a very prominent feature of acute nephritis, and a diet poor in nitrogen is strongly indicated. This period of retention is usually short; if it continues, it is very ominous. A few days' comparative nitrogen starvation will do no harm, and may avoid grave danger.

Von Noorden is of opinion that in acute and dangerous cases this is very necessary, and gives nothing but sugar, water, and fruit-juice for from three to eight days.

It may be noted here again that the degree of albuminuria gives no real clue as to the gravity of the condition. At my suggestion, Dr. F. W. W. Griffin examined the nitrogenous excretion in a series of cases of scarlatinal nephritis from the beginning. He found that, whereas there was a general relation between the amounts of water, urea, and total nitrogen excreted, there was none between these and the amount of albumen excreted. He concluded that the albumen afforded no more than a danger-signal at the commencement of the condition, and could not be accepted as a trustworthy indicator of the excretory capacity of the kidney.

The Use of Diuretics in Bright's Disease.—This question is really inseparable from the consideration of the treatment of albuminuria. There has always

been a tendency to regard 'flushing out' the kidney as a good line of treatment in Bright's disease; but before employing it we should consider what method of diuresis we mean to employ, how far such methods are desirable in the case before us, and how far they will achieve the end desired. Routine and indiscriminate 'flushing out' is to be condemned.

Methods of producing Diuresis.—The following are possible:

1. *By vaso-dilatation in the kidney*, as by the caffeine group of drugs. These probably act as direct stimulants to the renal epithelium, the vascular change being secondary.

2. *By vaso-constriction elsewhere*, in consequence of which the blood-pressure is raised and more blood is forced through the kidney—*e.g.*, digitalis.

3. *Increase in quantity of circulating fluid*—
 - (a) by absorption of water from the intestine, as by giving the patient large quantities of fluid to drink;
 - (b) by increasing the osmotic pressure of the blood. The saline diuretics, citrates, acetates, etc., act in this way, attracting water from the tissues into the blood-stream.

How far are these methods desirable in nephritis?

1. Why stimulate a damaged structure? I believe I have seen caffeine, theobromine, and diuretin all produce bad effects. It is chiefly in chronic parenchymatous nephritis that one sees them employed, and there is a danger that they will cause a return of acute symptoms; hæmaturia not infrequently follows.

I have gradually come to the conclusion that this group of drugs is unsuitable for nephritis, and should be restricted to cases where diuresis is required and the kidneys are not organically diseased.

2. Digitalis: as the blood-pressure is already raised, why raise it any further? I recently saw a case of chronic interstitial nephritis with dilating heart, which was causing a diminished urinary secretion. Digitalin injections were being given. I took the blood-pressure, and found it was 200 millimetres. The patient's whole difficulty was that the heart could no longer work against such high blood-pressure. The effect of the treatment was to load an overworked heart still more. I suggested nitro-glycerine and strophanthus instead; the pressure fell, and the patient was relieved for the time. I believe the unsatisfactory results, which some say digitalis gives them, are due to its being employed in unsuitable cases such as this. It is, indeed, difficult to see how digitalis could be a satisfactory diuretic in cases of nephritis.

3. In acute nephritis it is really no good to give large quantities of water with the idea of flushing the kidney, for the kidney cannot excrete it, so that it accumulates in the tissues, increasing the œdema.

This defective adjustment of the kidneys to varying water-supply is an important clinical point, as the following example, quoted by von Noorden, shows: A normal individual with an average hourly diuresis of 52 c.c. excreted an average of 723 c.c. for three hours after drinking 1,800 c.c. of Salvator water;

under the same circumstances, a patient, with acute nephritis, excreting 91 c.c. hourly before, only passed 103 c.c. after. Spontaneous diuresis is the first and surest sign of convalescence.

The attempt to increase the urinary flow by increasing the osmosis into the blood is less open to objection in acute nephritis. Citrate of potassium renders the urine less acid and, therefore, less irritating to the kidney. As the extra water is drawn from the tissues it will tend to diminish, and cannot increase the œdema.

I would put it this way :

(a) *In acute nephritis* we cannot flush out the kidney, because the inflamed organ will not respond. I believe that potassium citrate is the best drug, because it does not irritate the kidney, and any diuretic effect it may have is at the expense of the œdema.

(b) *In chronic parenchymatous nephritis* the kidney is more responsive, but it is undesirable to increase its secretion, either by irritating it by caffeine and the like or by increasing the already raised pressure. Yet diuresis is here certainly desirable, because, as I have noted, the total excretion of urea follows pretty closely the excretion of water. Here again potassium citrate seems to be freest from objection. Another mixture I have employed, and, as far as I can judge, with success, is :

Liq. ferri acetat.	℥ xv.
Liq. ammon. acetat.	ʒij.
Aq. camph.	ad ʒj.

(c) *In chronic interstitial nephritis* the kidney responds quickly to altered intake of water. But some years ago von Noorden claimed that, rather than trying to flush out the kidney, it was desirable to restrict the fluids to $1\frac{1}{2}$ litres a day. He maintained that this did not diminish the urea excretion, while the work of the heart was spared. He considered that the polyuria was secondary to polydipsia. I have tried this plan in a good many cases since, and am inclined to agree that it is preferable to the flushing-out method.

To draw the main conclusions arrived at in this chapter.

Oxaluria, if the result of taking foods rich in oxalates, will probably merely cause smarting micturition, perhaps albuminuria, or even hæmaturia. If the result of an intestinal intoxication, it will occur in crises associated with neurasthenic and neuralgic symptoms. The former group should be treated by limiting the intake of oxalates and giving potassium citrate and magnesia, the latter group by treating the intestinal fermentation and limiting the intake of sugar. Formation of oxalates in the tissues does not occur in sufficient amount to cause symptoms.

Phosphaturia.—If triple phosphates are present, they are due to ammoniacal decomposition, as in cystitis. If earthy phosphates are deposited, they are usually only the result of diminished acidity, the treatment consisting of inorganic acids and nervine tonics. A genuine excess of earthy phosphates may

occur as a symptom, and a relatively unimportant one, of wasting diseases.

Albuminuria.—The 'functional' albuminuria of young males is largely due to a defective vasomotor control, but there is also a hæmatogenous factor in it. By increasing the viscosity of the blood by calcium lactate we can control this latter factor, and thereby readily distinguish the condition from organic albuminuria.

In organic albuminuria too much attention has been paid to restriction of special forms of protein in the food—*e.g.*, eggs. The diet has much less to do with the albuminuria than has been supposed. Moderation in protein is advisable for a nephritic, because we all take more protein than is absolutely demanded for tissue-building. The excess is turned into urea and excreted, which is taxing a damaged organ unnecessarily. We can allow our chronic nephritis cases a much greater variety in diet so long as we avoid nitrogenous excess. In acute nephritis there is a tendency to nitrogenous retention, and therefore the protein intake should be greatly restricted.

Diuretics are of limited application in nephritis. In no case are those advisable which act by raising the general blood-pressure or by irritating the kidney. In acute nephritis the power to excrete water is greatly diminished, despite drugs; in chronic interstitial nephritis restricted fluids are preferable, for diuresis is already excessive. It is in chronic parenchymatous nephritis that diuretics are most serviceable.

CHAPTER VI

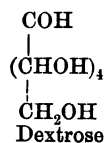
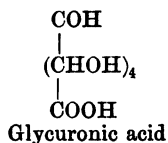
GLYCOSURIA AND DIABETES

A MEDICAL man is often faced with the problem of having to decide whether a patient is suffering from diabetes when his urine reduces Fehling's solution.

At the outset we may consider the principal substances other than sugar that might be responsible for the reduction.

1. Uric acid and kreatinin may both cause reduction, and are normal constituents of urine. But they are never present in sufficient amounts to cause reduction, if we are careful to add only as much urine as we have taken of Fehling's solution.

2. Glycuronic acid is closely related chemically to dextrose, as is seen by comparing their formulæ :



The reason for its appearance in the urine would appear to be that it has combined, like sulphuric acid,

with putrefactive bodies or else with administered drugs, such as chloral, morphia, camphor, chloroform, antipyrin, antifebrin, or pyramidon. Its function in this connection would appear to be antidotal, the conjugated acid being harmless. In this way protection against certain toxic substances is obtained.

Glycuronic acid may be present in fresh urine without causing any reduction, when, of course, confusion will not arise. Boiling for some time with 5 per cent. sulphuric acid will render it strongly reducing, however. Should a reduction be given with the untreated urine, glycuronic acid can be distinguished from dextrose by its failure to ferment. If it is found in the urine of a patient not known to be taking one of the drugs mentioned above, the test for indican (p. 220) should be tried, for it may simply be due to an unusual absorption of putrefactive bodies which are thus rendered inert. But if indican is not found, the suspicion of drug habits on the part of the patient may justifiably be entertained.

3. Alkaptonuria may be responsible. This 'is not the manifestation of a disease, but is rather of the nature of an alternative course of metabolism, harmless and usually congenital and lifelong' (Garrod). The individual appears to be incapable of completely breaking down the tyrosin in the protein molecule, so that intermediate products, homogentisic acid and possibly uroleucic acid, appear in the urine. But the urine does not ferment, and may stain the linen brown. Ochronosis—blackening of the cartilages and

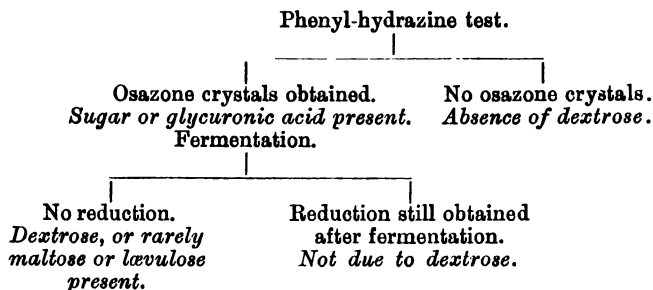
ligaments, and sometimes of the conjunctivæ—may occur. Usually there is a chronic arthritis also, which may lead to a curious 'goose gait.'

Other sugars than dextrose may be the cause of the reduction.

(a) Lactose is usually present in the urine during lactation, and occasionally during pregnancy. Any lactose reabsorbed from the mammary gland cannot be utilized by the tissues because it is a disaccharide, and all carbohydrates must be broken up in the intestines into monosaccharides before they can be assimilated. But alimentary lactosuria is also very easily produced in women who are suckling, showing that their capacity for metabolizing lactose is physiologically depressed.

(b) Pentose exceptionally occurs in the urine. Its presence is due to a congenital incapacity to metabolize the pentose sugars set free in the break-down of nucleo-protein. It may not reduce until the urine has been boiled for a few minutes, when the reduction takes place suddenly. It does not ferment, and may be further identified by the green colour it gives with orcin and hydrochloric acid. It is not a manifestation of disease.

If it be desired to prove that the reduction is due to dextrose beyond a doubt, the following scheme may be used :



Maltose gives a different osazone, while lævulose could be detected by the polariscope.

Before considering the significance of glycosuria, we must recall what a normal man can do with ingested sugar.

1. He can store it as glycogen.
2. He can store it as fat.
3. He can use it at once for muscular energy.

4. Any excess that cannot be dealt with in these ways will pass out into the urine. Anyone will have glycosuria after taking 150 to 200 grammes of *sugar* at one time. This may be considered to be 'physiological glycosuria.' But glycosuria after any quantity of *starch* is not physiological.

Von Noorden believes that the obesity which often precedes the onset of glycosuria in middle life is due to a loss in the power of glycogen storage, while the power of conversion into fat is still retained. The body will not allow a valuable food-stuff to escape if it can be avoided; therefore a stage of rapidly increasing obesity is met with, which he terms 'latent

glycosuria.' But this cannot be maintained indefinitely, and overflow of sugar into the urine will occur—consecutive glycosuria.

Experimental Glycosuria.—The experimental conditions under which glycosuria occurs may help to throw some light on the obscure problems of diabetes.

1. *Diabetic Puncture.*—When Claude Bernard discovered that puncture of the floor of the fourth ventricle would lead to glycosuria, it was hoped that the explanation of diabetes was not far off. But it was soon seen that this procedure merely led to a conversion into sugar of the glycogen stored in the liver. The glycosuria lasted only so long as the liver contained glycogen, and previous starvation would prevent its occurrence. More recently it has been found that previous section of the splanchnic nerve, or painting nicotine on the ganglia concerned, will prevent the impulses that produce the glycosuria from reaching the liver. Evidently the puncture sets up some nervous irritation, whether truly secretory or simply vasomotor in character, which leads to the emptying of the glycogen reservoirs.

The clinical equivalents of this process are seen in the glycosuria of concussion, cerebral tumours, pineal cysts, and the like.

I have come across several instances of cerebellar hæmorrhage, which on this account have been mistaken for diabetic coma. In one case, which was typical of the others, a man walking along the street suddenly felt so faint and giddy that he had to cling

to some railings. He was taken to a doctor, who gave him brandy and injected strychnine, whereupon he became unconscious. When he was brought to the hospital comatose, the house-physician passed a catheter and found sugar in the urine. He was treated for diabetic coma by bleeding and infusion of alkalies, but died in a few hours. At the post-mortem examination the urine in the bladder did not contain sugar, and a hæmorrhage was found in one lobe of the cerebellum, which had pressed on the fourth ventricle. I have seen the same thing in a lenticulo-striate hæmorrhage, where the blood had been effused into all the ventricles. In the case here related the sudden onset was unlike that of diabetic coma; but the mistake is very liable to occur in hospital practice when a patient, already comatose, is brought in by the police and no clinical history can be obtained. Under such circumstances the test for diacetic acid with perchloride of iron becomes of paramount importance, for it will always be found in diabetic coma, while it is absent in this type of glycosuria.

2. *Phloridzin Poisoning*.—It is well known that phloridzin will produce glycosuria, and that it does so by its action on the kidney tubules, for if injected into one renal artery the glycosuria occurs sooner, and to a more marked degree, on that side. But the only point of interest in this type of glycosuria to us now is that it provides an example of sugar formation from a non-carbohydrate source, since its excretion continues after all the carbohydrate in the body has

been used up. That protein is the main source of the sugar is shown by the marked and constant rise in the nitrogenous output that accompanies it.

3. *Asphyxial Conditions*.—This, according to Edie, is due not to lack of oxygen, but to excess of carbon dioxide. In the concentration necessary to effect this, carbon dioxide is really an anæsthetic. Sugar, as distinct from glycuronic acid, has been found in the urine after other anæsthetics.

4. *Hormones*, such as adrenalin and thyroid extract, may cause glycosuria. In the former case a direct action on the pancreas has been held responsible by Herter, because it has followed the painting of minute doses of adrenalin on the pancreas. A difficulty in the way of this view is that whereas, according to Noel Paton, excision of the pancreas does not cause glycosuria in birds, adrenalin does, so the drug can hardly act through the pancreas. Another view is that the adrenalin, by acting on the sympathetic, is an irritant preventing carbohydrate storage. There is not at present sufficient evidence to settle the point.

Glycosuria from excess of thyroid juice is seen both in exophthalmic goitre and on administration as a drug. Lorand's view that this is the cause of true diabetes has not much to support it. There is a practical deduction to be drawn, as we have seen, as to the unsuitability of thyroid extract in the treatment of obesity, for these cases may be examples of 'latent glycosuria.'

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5. *Excision of the Pancreas.*—The experimental data will be found in Chapter III., on page 103. Lancereaux was the first to maintain the association of pancreatic disease with diabetes. Fibrosis is the most common change to find in the pancreas in severe diabetes, according to Opie, the intralobular variety of pancreatitis being the most characteristic lesion. It is certain that the pancreas may be the site of malignant or cystic disease without diabetes. There must be a more extensive destruction of the secreting tissue than usually occurs under such conditions. It must be admitted that in many cases of diabetes there is really no evidence of structural change in the pancreas.

Rose Bradford has recorded a case in which a large pancreatic tumour was found at an exploratory laparotomy. Three years later the patient again came under observation, suffering from diabetes of a severe type, and the tumour could no longer be detected. He thinks this was a case of chronic pancreatitis, with subsequent atrophy of the gland leading to diabetes. It is possible that former attacks of pancreatic disease may have been responsible for diabetes, even though no evidence of the existence of such may be forthcoming at the time. Systematic inquiry for a history of severe 'dyspepsia' or jaundice may help to elucidate this point.

We can hardly venture to claim yet that all cases of 'essential' diabetes are of pancreatic origin, but with increasing knowledge we shall probably be able

to allot to the pancreas a still larger rôle in its production.

In discussing the relationship of the pancreas to diabetes in a previous chapter, the conclusion was reached that the loss of an internal secretion produced by the pancreas, though not necessarily in the cell islets, explained the facts best. Without accepting all Pavy's views on carbohydrate metabolism, the hypothesis he has recently put forward, as to the mode in which this internal secretion may act, is worthy of careful consideration. There is no such thing as impermeability of the kidney to sugar; where the water molecule can go, molecules of crystalloids not much larger than that of water will follow. Something must link this small molecule of sugar to a larger one. Just as the oxygen is linked to the hæmoglobin, so the sugar is linked to protein. But something must provide the link, or, in other words, provide an amboceptor. This is the work of the internal secretion of the pancreas. I would further point out, in this connection, the position on the circulation in which we find this secretion poured in. It would seem as if the ingested carbohydrate in the porta vein, meeting this amboceptor, was then and there attached to larger molecules, while the sugar in excess of the immediate requirements of the tissues was stored up in the liver as glycogen. Even in a healthy person, a sudden rush of ingested sugar may overtax these mechanisms, and unattached sugar molecules overflow into the urine. If the amboceptors

are deficient, there will be this overflow after the ingestion of an ordinary carbohydrate meal—alimentary glycosuria. If the amboceptors are very gravely deficient, not only will the sugar from the food appear in the urine, but the sugar from the tissues will also pass into the urine.

The probable mechanism by which this takes place is as follows: The tissues are now in a condition of sugar starvation, and in starvation the autolytic enzymes come into play. By the break-down of the cells fresh sugar molecules are set free, not merely from glyco-proteins, but from amino groups like alanin in the true protein molecule.

These are equally unable to be used by the tissues which need them, because the combining link is missing. The increased nitrogenous output in these cases is a proof of the increased katabolism which is going on. That the essential feature is the failure of the tissues to utilize carbohydrates is shown by the fact that the respiratory quotient $\frac{\text{CO}_2 \text{ expired}}{\text{O}_2 \text{ inspired}}$ (which is normally increased by a carbohydrate diet) is depressed in the diabetic, and is not appreciably increased by the ingestion of carbohydrates in severe cases.

The crux of the situation is that mild cases may become grave if deluged with carbohydrate, while severer cases may acquire a limited tolerance for carbohydrate if properly regulated—that is to say, the types shade off into one another. This suggests

some cause which is capable of quantitative alterations. A varying number of amboceptors produced by the pancreas would account satisfactorily for these phenomena.

That there is a mild stage without symptoms is proved by the way in which examiners for life insurance find glycosuria in young proposers for policies. There seems a curious liability for a potential glycosuria to become actual under the stress of examination for life insurance.

Some years ago I was asked by a colleague to confirm the presence of dextrose in the urine of a man whom he had examined for life insurance. Typical osazone crystals were easily obtained; yet the applicant had specially been examined by his own medical man the day before, in order to see if he could pass the ordeal successfully, with a satisfactory result. Accordingly, he was greatly surprised when he was told he was glycosuric. On a subsequent examination he was free from sugar without having undergone any special dieting.

Recently I was asked to see a young man of twenty-one, in whom glycosuria was found on three separate occasions when he was examined for life insurance. On the last occasion he had undergone a previous dieting at the hands of his own doctor, with the hope of deceiving the examiner, but in vain. Yet only on one occasion had his own doctor been able to find sugar. When I saw him he was on a carbohydrate-free diet, and I found no sugar. I

directed him to take an ordinary dinner that night, and bring me the urine passed on getting up in the morning. It contained undoubted dextrose ($2\frac{1}{2}$ per cent.), together with some lævulose, as is not uncommon in alimentary glycosuria. Yet at no time did he pass acetone bodies even when he was strictly dieted. This might be regarded as a mild case; but in a thin, fair-haired youth of twenty-one a very guarded prognosis was indicated. If it had not been for the insurance examination, the glycosuria would have remained unsuspected until the onset of some marked symptom, and then in all probability dieting would not have been successful in removing the sugar from the urine.

In this connection it may be noted that if an examiner for life insurance finds acetone bodies present in the urine without sugar, he should at once suspect that dieting has been practised with the view of enabling a glycosuric to pass muster. A test-meal of 3 ounces of sugar dissolved in water should be given, and the urine tested again an hour later. This is useful also in cases of suspected alimentary glycosuria without the question of attempted fraud.

There would be general agreement, I suppose, in designating the following as examples of mild and severe cases of glycosuria respectively. It would be a mild case if the patient were over forty and not wasting, his tongue not raw, though perhaps covered with a black 'hairy' fur. The urine would contain no acetone bodies. Restriction of the diet would cause

sugar to disappear quickly ; probably acetone bodies would make a brief and slight appearance now, but so they would in anyone on a suddenly restricted diet. Exercise would cause a diminution of the glycosuria, which shows that sugar could still be utilized by the tissues, and that it was mainly a question of deficient power of storage. A typically severe case would be one in a patient under thirty, who was wasting and had a raw 'beefy' tongue. The knee-jerks might be absent. Diacetic acid would be present in the urine, and sugar still present on a restricted diet. Acetone and diacetic acid would be markedly and persistently increased by a sudden restriction of the diet, and exercise would cause an increase in the glycosuria, indicating that the body was unable to utilize even the sugar set free from the break-down of its own tissues.

If we had merely to deal with two such distinct classes as these, there would be little difficulty in distinguishing between so-called alimentary glycosuria and diabetes. But, unfortunately for the classifier, all shades of intermediate cases are encountered. Beddard divides these into two main types :

(a) Passing from mild to severe. The urine, originally sugar-free on a restricted diet, contains sugar, at first intermittently, then continuously. This change may be brought about acutely and permanently by a carbohydrate debauch, anæsthetics, intercurrent disease, or mental strain.

(b) Passing from severe to mild. This is less

common; they do not lose their sugar within a week of receiving a strict diet. At first under treatment their urine may show a very definite diacetic acid reaction; but this disappears completely, the sugar in the urine slowly falls, and at the end of a month, or a great deal longer, disappears altogether. But such a good result is not necessarily permanent, and a marked change for the worse may rapidly follow a return to ordinary diet.

Association of Albuminuria with Glycosuria.—There are two conditions in which we may meet with both albuminuria and glycosuria, and the relative importance of the abnormal constituents of the urine is quite different in each.

(a) A patient with granular kidney is very likely to be 'gouty,' and as such may have glycosuria more usually of the amenable type. I have seen a striking example of the way in which the glycosuria may mask the more important symptoms of the nephritis. A man who had both albumen and sugar in his urine developed tingling, numbness, and some loss of power in the left side, and became drowsy. His doctor feared that diabetic coma was impending. When, however, I found that there was no diacetic acid in the urine, but that the volume of the urine was diminishing, that the blood-pressure was high, and the aortic second sound was greatly accentuated, I concluded that it was uræmia rather than diabetic coma that was to be feared. Vigorous treatment was directed towards lowering the vascular tension, and

the glycosuria was ignored for the time being. Rapid improvement followed.

(b) Prolonged glycosuria almost inevitably leads to albuminuria in time. Pavy regards it as the result of irritation of the kidney. As long as it does not cause a rise of blood-pressure, cardiac hypertrophy, or other evidence of arteriosclerosis, one need not trouble very much about the albuminuria. The treatment is merely that of the glycosuria.

The condition of the vascular system and the diacetic reaction will be a better guide as to which of these two types we have to deal with than the amount of the sugar compared with the amount of albumen.

The appearance of casts in the urine of a diabetic should, however, always be regarded as serious. Von Noorden states that they have never yet been found where there is no acidosis, and according to some they are the direct result of irritation by acids. These casts have nothing to do with the intensity of the albuminuria; on the contrary, they are often present when the albumen can only just be detected by the most delicate tests. They may be prognostic of coma, and should be looked upon as a danger-signal. But all this is perhaps straying beyond the limits of physiological principles. The principles previously laid down, however, provide us with some guides to—

Treatment.—The ideal to be aimed at is a regulation of the diet to a point at which both sugar and diacetic acid are absent from the urine. We have

seen that in the severer cases these two aims are in a sense antagonistic. If it be impossible to accomplish both, I would prefer the patient to pass sugar rather than diacetic acid, for the latter implies starvation, if not intoxication. As Walker Hall expresses it, the diabetic has to sustain a big output with insufficient capital. A large regular intake is therefore an absolute necessity. Under-nutrition is his greatest danger.

We will assume that possible fallacies as to the presence of other substances than dextrose have been eliminated, and that gross lesions of the pancreas and cerebral diseases have as far as possible been excluded. The sugar is estimated from a twenty-four-hour specimen while on an ordinary diet, and diacetic acid and acetone are tested for. If they are present, we know that we have a severe case to deal with.

The next step is to cut off the sugar in the diet, but not the starch at present. If sugar is still found in the urine, the condition is definitely pathological.

Now the starches are cut off gradually; if the urine is not free from sugar in a week from the giving of a strict diet, and if the acetone bodies make more than a transitory appearance, the case must be regarded as definitely diabetes.

Since almost all diabetics have some degree of tolerance for carbohydrate, and since total deprivation of carbohydrate will lead to acetonuria in anyone, it is important to determine as accurately as possible what that degree of tolerance is in the case under

consideration. For this purpose some standard diet is necessary of known carbohydrate content. The following is the one suggested by Von Noorden :

Breakfast.—Coffee or tea, with 1 to 2 tablespoonfuls of thick cream, 6 ounces ; hot or cold meat (weighed after cooking), 3 ounces ; butter ; two eggs with bacon ; white bread, 2 ounces.

Lunch.—Two eggs (cooked as desired, but without flour) ; meat, about 6 ounces ; vegetables, such as spinach, cabbage, cauliflower, asparagus, prepared with broth, butter or other fat, eggs or cream, but without flour ; cheese and butter, 1 ounce ; two glasses of light wine ; one cup of coffee, with 1 to 2 tablespoonfuls of thick cream ; white bread, 2 ounces.

Dinner.—Clear meat soup (with eggs or vegetables) ; one or two meat dishes, with vegetables, salad of lettuce and tomatoes ; wine ; no bread.

Drinks.—One or two bottles of aerated waters.

If these 100 grammes of bread do not cause any glycosuria, then the bread is gradually increased until sugar appears. If sugar does appear with this test diet, then the diet may be continued for a few days until the sugar is constant, and the bread then diminished.

Even supposing that in a severe case we are unable to render the urine free from sugar, we can probably find a point to which the intake of carbohydrate can be raised without increasing the glycosuria while diminishing the acetonuria. This will be the best point at which to maintain this patient's metabolism

if further restriction produces a fall in the amount of sugar, it is not beneficial if it causes a return of acetonuria. After a time, say six weeks, the diet may be cautiously relaxed, if the urine has become sugar-free.

We can assist the patient to reach as high a 'toleration point' as possible in two chief ways:

(a) By choosing those forms of carbohydrate which he can utilize, and by studying the effect of exercise on the excretion of sugar, and regulating it accordingly.

(b) By diminishing the production of the acetone bodies.

Both these points are considered in the chapter on Acetonuria and Acid Intoxications. We may state briefly here that the power of a diabetic to assimilate lævulose rather than dextrose is quite transitory, lasting a few days at the outside; that potato starch is usually much better borne than flour, and that oatmeal can sometimes be tolerated. The abiding difficulty is to obtain a satisfactory substitute for bread. Osler tersely says: 'Of the gluten foods, many are very unpalatable, others are frauds.' A drop of iodine solution on the bread will quickly detect a fraud by the well-marked blue colour it yields. The protene diabetic breads are sometimes tolerated when gluten breads cannot be taken.

To diminish the production of the acetone bodies, the ingestion of the lower fatty acids should be avoided. The butter should be well kneaded in cold water before being eaten. The drain of bases should

be prevented by administration of calcium and magnesium salts. Citric acid should be given up to 20 grammes (5 drachms) a day if necessary, to diminish the break-down of the fats of the body.

Though drugs may help to prevent the appearance of the acetone bodies, they have but little effect in preventing glycosuria. In so far as they have any effect, we are entirely ignorant of the way in which they act, and therefore they do not really come into our present discussion. The general consensus of opinion seems to be that codein is the most effective in the severer cases, salicylate or aspirin in the milder cases. Personally I have never observed any benefits that could be ascribed to any other drugs. A great objection to the salicyl groups of drugs is the way they mask the important diacetic reaction, since the urine will now give a deep purple colour with perchloride of iron.

In this brief review I have attempted to deal with principles rather than with details of treatment, important though these undoubtedly are, because they are generally fully considered in handbooks of treatment. But to employ those details intelligently a clear grasp of the underlying principles is essential.

If it be objected that I have not succeeded in drawing a sharp line of distinction between the cases of mild glycosuria and severe diabetes, my plea must be that Nature has not done so; it is all-important to realize that a carbohydrate debauch may precipitate a mild and amenable case once and for all into the severe and intractable category.

CHAPTER VII

ACETONURIA AND ACID INTOXICATIONS

It has long been known that acetone appears in the urine and in the breath of a diabetic patient who is progressing unfavourably. In fact, its presence is a better gauge of the patient's condition than the amount of sugar in the urine. But more recently it has been recognised that this symptom appears in a great many other conditions, such as the recurrent vomiting of children, the pernicious vomiting of pregnancy, broncho-pneumonia, fevers, carcinoma of the digestive organs, prolonged rectal feeding, and after anæsthetics. It is also stated to occur in uræmia, but I have never found it, though I have examined carefully for it in several cases.

What general significance is to be attached to a symptom appearing under conditions apparently so diverse?

I. The Significance of Acetonuria.

Acetone comes from the unstable diacetic acid. If this abnormal acid is being excreted slowly, it will all break down into acetone. But if more than

$\frac{1}{2}$ gramme of acetone is being excreted in a day, diacetic acid is certain to be found also.

The odour, variously compared with that of hay or of apples, which is noted in these cases is due to diacetic acid rather than to the acetone, which has a more penetrating odour.

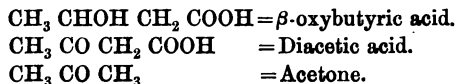
It follows that the recognition of the diacetic acid in the urine is of greater importance than the detection of acetone, its decomposition product, and this is convenient, for diacetic acid is very easily detected. On the addition of ferric chloride, a claret colour results, which (unlike the somewhat similar colour seen on addition of this reagent to the urine of patients taking salicylates or carbolic acid) does not appear if the urine has been previously boiled.

Acetone is best detected by adding a few drops of a freshly prepared solution of sodium nitro-prusside to the urine, and then pouring some strong solution of ammonia on the top. A magenta-coloured ring appears at the line of contact, and diffuses upwards.

Diacetic acid in its turn is usually derived from β -oxybutyric acid. There is no convenient clinical test for this body,* but it is probably present when the diacetic reaction is well marked. This is, however, not necessarily the case. It sometimes cannot be found in diabetic coma, and it may be absent in the

* After fermentation to remove the sugar, the concentrated urine is distilled with strong sulphuric acid, and the distillate examined for crystals of α -crotonic acid. β -oxybutyric acid is lso lævorotatory.

acetonuria of broncho-pneumonia. The chemical changes involved are simple. β -oxybutyric acid yields diacetic acid by oxidation, while diacetic acid is converted into acetone by the loss of CO_2 ; thus



It is quite probable that β -oxybutyric acid is a normal metabolic product, but diacetic acid has never been found in normal urine. This would appear, therefore, to be the point of divergence between the healthy and abnormal processes. The further change from diacetic acid to acetone can hardly be prevented.

So far as we know, then, *the immediate precursor of acetone is a fatty acid*. What is the source of the fatty acid?

The sudden and complete withdrawal of carbohydrates from the diet of a diabetic patient is known to be dangerous. It is followed by nausea, vomiting, loss of weight, the odour of acetone in the breath, the presence of these acids in the urine, and a great increase in the amount of ammonia in the urine. Though the total amount of nitrogen is not altered, the ammonia is greatly increased. Signs of coma may also occur. In one case it is recorded that the ammonia increased from 7 to 29 per cent., and that the blood also became less alkaline. Then the patient was given more carbohydrates, and these symptoms disappeared. A great improvement took place in the

general condition of the patient, including the disappearance of the smell of acetone in the breath and the diminution of the ferric chloride reaction of the urine, although there was no marked change in the amount of sugar excreted in the urine.

It is therefore clear that these bodies do not come from carbohydrates, because carbohydrates diminish the amount of them in the urine. Do they come from protein or from fat? Both views have been held, but it is certain that protein cannot be the main source, for their excretion is not accompanied by a proportionate increase in the excretion of nitrogen and sulphur.

It is possible, however, that some of the fatty acid groups in protein, such as leucin, can give rise to acetone bodies. It has been shown that leucin increased the output of both acetone and β -oxybutyric acid in a diabetic and in a normal man deprived of carbohydrates.

But it is to the fat chiefly we must look as the source of acetone, and as acetone is derived from the decomposition of a fatty acid, this would involve only a simple change.

Geelmuyden and others produced acetonuria in healthy persons by a fatty diet. In one case, the sole diet, daily for five days, was 250 grammes of butter, 200 grammes of oil, and a little wine. As a result β -oxybutyric acid, diacetic acid, and acetone were found in the urine in amounts such as only occur in the severest cases of diabetes. On the last day these

acids caused 37 per cent. of the total nitrogen to appear in the form of ammonia.

The Element of Starvation.—Anyone can produce acetonuria by starving himself. In some diseases associated with acetonuria the element of starvation is obvious—for instance, in carcinoma of the digestive organs, certain febrile conditions, and in prolonged rectal feeding. A wasting diabetic is being starved also from inability to metabolize carbohydrate.

Of all the tissues, the fat loses most in starvation, the more noble organs being fed at the expense of the less essential ones. To effect this, the fat must be broken down, in the course of which fatty acids would be set free.

The Element of Defective Oxidation.—Oxygen starvation can produce a similar effect. Thus in mountain-sickness, in which deficiency of oxygen pressure is the exciting cause, acetonuria occurs. Oxygen starvation is obviously at work also in broncho-pneumonia.

Von Noorden correlates these factors by referring the rôle of carbohydrates in the prevention of acetonuria to the relative abundance of oxygen they contain. In the complex changes which occur in the metabolism of the tissues this oxygen is drawn on to complete the break-down into CO_2 and water. In its absence, these less completely oxidized fatty acids appear. That the acetonuria of febrile conditions could be largely inhibited by supplying the wasting tissues with carbohydrates he proved as

follows : In two cases of typhoid fever, he gave patient A a diet with very little carbohydrate in it, and patient B one with plenty of carbohydrate. A had a marked diacetic reaction, and B only a trace of acetone. After a few days the diet was reversed, with the result that the former showed only a trace of acetone, and the latter a well-marked diacetic reaction.

Meyer has made similar observations on children suffering from various acute infectious fevers.

I would suggest a slightly different and rather simpler way of regarding the matter.

Verworn thinks it probable that the oxidation processes of the tissues are carried out by non-nitrogenous groupings which are of a carbohydrate nature, and therefore contain aldehyde groups.

In the absence of either sufficient oxygen or of sufficient aldehyde groups to which the oxygen could attach itself, defective oxidation of the tissues must occur. Acetonuria, therefore, would be a symptom of incomplete oxidation due to interference with either factor.

Other substances besides carbohydrates, however, appear to be able to play this rôle ; tartaric, citric, and glutaric acids have all been shown to be capable of diminishing the output of acetone and β -oxybutyric acid. Hurtley and Bainbridge found that 20 grammes of citric acid daily had a marked effect in this direction. The benefits of citrates in diabetic acidosis have generally been explained as due to their becoming bicarbonates in the blood, and thus neutralizing the

abnormal acids. But evidently this is not the only way in which these substances act, for this explanation would not apply to glutaric acid.

Now, the organic acids of disordered metabolism have to be excreted, because they are not oxidized to CO_2 . Carbon dioxide can be removed without loss of bases, whereas unburnt organic acids must be excreted as neutral salts. This may be done by combining with ammonia or with fixed alkali. Acidosis, therefore, may be due to a shortage of fixed bases as well as to an excess of acids, and may be produced by a diet which is poor in salts, though otherwise adequate. In diabetes there is a prolonged drain on the calcium and magnesium salts, which must be a factor in inducing acidosis.

Acidosis and Acid Intoxication.—We must distinguish between acidosis, in which organic acids occur in abnormal amounts in the blood and urine, and acid intoxication, in which, in addition, toxic symptoms make their appearance. Are the symptoms produced by the fatty acids *per se*, or is the presence of these acids merely another symptom of perverted metabolism?

The acids are not themselves directly toxic. Given to man or animals, they do not even produce acetouria. But they might produce toxic results simply because they are acid, and thus upset the alkalinity of the blood,* diminishing its power of taking up CO_2 ,

* Alkalinity is here used in the accepted sense of 'titration alkalinity,' which indicates the power of the blood to neutralize weak acids. In the strictest language of modern physical chemistry, blood is neutral, having no excess of hydroxyl atoms.

and leading to internal asphyxiation of the tissues. This will actually occur if animals are repeatedly injected with acids, though carnivora have considerable power of neutralizing the acids by producing ammonia from their proteins.

But it has been urged that experimental acid intoxication is, perhaps, not strictly comparable to the acid intoxication of disease. Thus, though in diabetic coma the alkalinity of the blood is usually reduced, this is not invariably the case. According to Pembrey, Spriggs, and Beddard, the low percentage of CO_2 in the blood of comatose diabetics is not so much due to the blood being unable to combine with it (for outside the body his blood may still be able to take up a normal amount of CO_2), but is rather the result of the exaggerated respiratory movements. However, the total amount of abnormal acids excreted in the urine will be a better guide to the degree of acid intoxication than the composition of the blood at any one time, since the kidneys will attempt to keep the composition of the blood constant. Again, the exaggerated respiration must be due to excess of CO_2 in the respiratory centre, and indicates some difficulty in getting rid of it.

Acid intoxication may be said to occur at the point where the body fails to cope with the tissue disintegration, of which the abnormal acids are a sign, or to compensate for the drainage of alkaline bases.

Tissue degradation, or autolysis, is brought about by intracellular ferments whenever the food-supply

is insufficient for the needs of the organism. Consequently, the nobler organs can live at the expense of the others by utilizing the products of this ferment action.

Schryver has shown that this autolysis proceeds much more rapidly in fasting than in well-fed tissues. The products of autolysis fall into two groups, amino bodies and non-nitrogenous acids.

In well-nourished animals, the excess of ammonia, which is always present from protein disintegration, will neutralize the acids, the resulting ammonium salts being converted by the liver into urea. But in starvation, the fats being chiefly drawn upon, the non-nitrogenous acid groups will be formed in excess. These will appear in the urine as oxybutyric and diacetic acids.

If acetonuria as a symptom of tissue disintegration occur without acid intoxication, it is because the protective ammonia formation is sufficient. When once it becomes insufficient, both acetonuria and acid intoxication will result.

To recapitulate, acetonuria is the result of increased katabolism of fat itself, or of the fatty-acid groups in protein. This will occur in any starving tissue, but particularly if oxidation be deficient, because then the final breaking down of the fat into water and CO_2 does not occur. Deprivation, or non-utilization, of carbohydrates is specially likely to cause acetonuria, both because the tissues are being starved, and because the process of oxidation is apparently closely

connected with the carbohydrates. If the increased katabolism of fat is great enough to cause acid intoxication, the condition becomes much more serious. Acid intoxication may result either from abnormal production of acids or from deficiency of bases.

II. Symptoms associated with Acetonuria.

(a) *In Diabetes*.—The cardinal symptoms have already been dealt with, when considering the effect on a diabetic of sudden deprivation of carbohydrates. But milder manifestations of this sort are not infrequent in the more amenable type of diabetes. If 'bilious attacks,' accompanied by some drowsiness, occur, they will usually be found to be associated with the appearance of acetone and diacetic acid in the urine, though these bodies may have been previously absent.

The symptoms of diabetic coma are too well known to need restatement. It is a curious fact that there may be a decided drop in the acetone bodies just before and during the coma, which shows that the pathology of the condition is not yet fully explained.

(b) *In Recurrent Vomiting*.—In 1882, Gee called attention to cases of fitful and recurrent vomiting of unknown causation in children. Later observers noted acetone in the breath, urine, and vomit. Diacetic acid and oxybutyric acid have also been found when looked for. The analysis of fifty-five cases by Batty Shaw and Tribe gives the following clinical

features: The cases usually occur between three and eleven years of age. The frequency of the attacks is very variable, a common interval being three months. There may be a prodromal period, in which dyspnoea, sighing respirations, offensive breath, choreic movements, and general restlessness have been noted. The tongue may either be coated or clean. Then vomiting begins, without nausea, and usually without gastric pain, all food is rejected, and towards the end of the attack bile appears, sometimes even blood. Constipation is common. The attacks may last only a few hours, but the average duration is five or six days. It is the rule for fever to occur during the attacks of vomiting. Wasting is often a very marked symptom. In later life these attacks are sometimes replaced by migraine, but they tend to disappear when puberty is reached. Three of the fifty-five cases were fatal. A mild degree of such a condition is, I believe, quite common in children, and I would venture to suggest that 'biliousness,' which, as Gee says, is a real state, a very common state, but a state that is little understood, is really of this character also. Probably the liver is put out of work by some toxic substance absorbed from the intestine. This would explain why the prompt use of a mercurial purge may ward off an attack. When once the liver fails to do its work, the tissues are starved, and, in their autolysis, produce these abnormal acids. The vomiting accentuates the condition by increasing the starvation and the loss of saline bases.

(c) *In the Pernicious Vomiting of Pregnancy.*—

It is now recognised that, though the pernicious vomiting of pregnancy may be due in some cases to mechanical causes, such as displacement of the uterus, and in others to neurotic causes, there remains a more serious group in which a toxæmia is responsible. In these toxæmic cases, necrosis and degeneration of the central portion of the liver lobule, and necrosis of the excretory portions of the kidney, have been found by Whitridge Williams. He found also a striking increase in the percentage of nitrogen, eliminated as ammonia, which, compared with the total nitrogen of the urine, amounted to 16 to 32 or 46 per cent., instead of the normal 3 to 5 per cent. He suggested that this might be due either to failure of urea formation in the liver, or to the attempt to neutralize acid intoxication.

Dr. Helen Baldwin found, in such a case, that the urine yielded a marked reaction for acetone and diacetic acid, but no sugar. The patient's condition was so serious that labour was induced. After this the abnormal acids diminished, until only acetone was found. On the tenth day after the induction of labour there was a return of severe headache, nausea, and vomiting, and it was noteworthy that, on this day, diacetic acid was again found in the urine. After this recovery was uninterrupted.

But Williams' interpretation of these facts is open to several objections. A very small proportion of the liver substance is sufficient to carry out the conver-

sion of ammonia into urea. Extensive necroses have been produced experimentally in the liver without raising the percentage of ammonia. In phosphorus-poisoning the high ammonia percentage may be reduced by sodium bicarbonate, pointing, not to a defective formation of urea, but to the excretion of acids that should have been converted into CO_2 .

In starvation from any cause, the percentage of ammonia increases. This is mainly due to a drop in the urea excretion, which must occur since so much of the urea is derived directly from the nitrogenous food. Now, the absolute amount of ammonia nitrogen in Williams' first case during the vomiting was 1.44 grammes, while a month after labour had been induced it was 1.21 grammes. These differences are not so great as those observed by Cathcart in a professional faster, in whom the ammonia nitrogen was 0.6 gramme before and 1.4 grammes during the fast.

Again, the total nitrogen output in Williams' cases was lower than that found by Cathcart in his fasting man and that which I have found in cases of hæmatemesis receiving saline enemata only.

When ammonia is expressed in percentages, these important facts are obscured, and an ammonia coefficient reaching to 32 or 46 per cent. is apt to acquire an undeserved significance.

Leathes puts it very fairly when he says: 'Before it can be safely maintained that these high figures are a sign in themselves of a toxæmia that is likely to prove fatal unless the most active measures be

taken, it is necessary to prove that they are not sufficiently accounted for by some of the attendant circumstances of the patient's condition—the low nitrogen content of the absorbed food, the imperfect nutrition due to the incessant vomiting, the loss of alkali in the vomit, aggravated possibly by the requirements of the foetus.' In other words, the high ammonia coefficient may result from simple starvation, rather than from an attempt to neutralize acids.

(d) *In Gastro-intestinal Acetonuria.*—I saw a good example of this in a lady, aged twenty-four, who consulted me for rapid wasting with marked constipation and occasional vomiting. She only weighed 5 stone 6 pounds, and all the ordinary causes of wasting could be excluded. In a fortnight she had lost two pounds more. Diacetic acid was found in the urine, but no sugar or albumen. Then membranous casts were found in the stools. I ascertained that she had been taking an extraordinary diet—large quantities of beef-tea, mushrooms, and extractives of all sorts. There was very little nourishment in the diet, but a large amount of stimulating substances. The treatment was simply to regulate the bowels, and to give her a plain but liberal diet, with alkalis before meals, and 20 grains of citrate of potassium three times a day. The diacetic acid soon disappeared, and the patient rapidly gained weight—1 stone in six weeks. Two years later I heard that she was perfectly well. Apparently membranous colitis had caused both the emaciation and the

acidosis, and the condition had been accentuated by faulty diet.

(e) *In Broncho-pneumonia*.—Garrod associates the symptoms of drowsiness, torpor, and vomiting with the presence of acetone and diacetic acid in the urine.

The principal symptoms, then, which seem to be commonly associated with the various forms of acetonuria are wasting, vomiting, drowsiness, and coma.

Post-Anæsthetic Acetonuria.—We are now in a better position to consider this vexed question. That death might follow the delayed action of chloroform was first suggested, so long ago as 1850, by Casper, and then by Langenbach. In this country, Leonard Guthrie drew attention to the condition in 1893, and lately much interest and discussion has been aroused on the subject. Other anæsthetics besides chloroform have produced the symptoms.

Twelve hours or so after the anæsthetic the patient (usually a child) suffers from profuse and repeated vomiting, the vomiting eventually resembling the dregs of beef-tea. Sometimes there is a preliminary period of restless excitement and delirium.

This is followed by drowsiness, apathy, and unconsciousness, deepening to coma. Death usually occurs about the fifth day, but sometimes later, from cardiac or respiratory failure, gradual or sudden. Pyrexia is not marked as a rule, though the temperature may be very high just before death. The pulse becomes very rapid. Albuminuria and the presence

of casts in the urine are common. Furthermore, there is a smell of acetone in the breath, while acetone and diacetic acid are found in the urine. It will be noted that these symptoms resemble in essentials the features of other acetonurias; but the abnormal substances are only looked for, as a rule, after anæsthetics where something goes wrong. Routine examinations, therefore, are necessary before we can decide what weight can be attached to their presence in these cases. Such have been made, but the results are quite discordant.

Hubbard, in 135 surgical cases, found acetone nine times, with diacetic acid four times. In another series of seven cases, acetone or diacetic acid was found, on being looked for to explain some irregularity in convalescence. Telford and Falconer obtained the following results in their cases :

	Acetone present.	Diacetic Acid present.
	Per Cent.	Per Cent.
<i>Pre-anæsthetic examination :</i>		
Non-septic cases (110)	4.5	7.3
Septic cases (33)	36.4	30.4
<i>Post-anæsthetic examination :</i>		
1. Chloroform alone (38)	92.1	84.2
2. Chloroform introduced by ethyl chloride (53)	88.6	81.1
3. Ethyl chloride alone (18)... ..	83.3	66.6
4. Ether (9)	88.8	77.7

On the other hand, in 1905, Mr. W. G. Ball, while house-surgeon at the Metropolitan Hospital, kindly

examined for me, before and after the anæsthetic, the urines of all the cases operated on during a period of three months, without finding diacetic acid once. Recently he has repeated such examinations at St. Bartholomew's Hospital on forty cases, in which various anæsthetics were employed, chloroform being the commonest. In no case was diacetic acid detected.

Such extraordinary discrepancies as exist between these results and those of Telford and Falconer perhaps depend on some difference in the method of administration. The difference in the experiences at different hospitals as to the frequency of post-anæsthetic poisoning may be due to a similar reason. High percentage of the anæsthetic vapour has a much more injurious effect upon protoplasm than a low one. In any case, it must be conceded that acetone and diacetic acid appear frequently after anæsthetics without toxic symptoms.

The most striking change noted post-mortem is fatty degeneration of the liver, sometimes so intense as to give rise to a 'canary yellow' appearance. Fatty degeneration has also been noted in the heart, kidneys, and gastric mucous membrane.

Two interpretations have been given :

1. The anæsthetic is the primary cause of the fatty degeneration (Stiles and MacDonald, Carmichael and Beattie).

2. The anæsthetic is merely the 'last straw,' causing a fatal result by acting on a previously fatty or (Guthrie).

The difficulty about the first view is that there is no relationship between the symptoms and the amount of anæsthetic employed. In the same patient, the anæsthetic may have been taken well on one occasion, while, on a second, a very much smaller amount has been fatal. Idiosyncrasy will hardly explain this.

It must be admitted that prolonged administration of chloroform can produce a fatty liver, but it seems almost incredible that such small doses as have sometimes caused the symptoms can do this. In one recorded case the liver could be felt three fingers' breadth below the costal margin twenty-four hours after the administration of a small dose.

Guthrie's view would explain why anæsthetics should be dangerous at one time and not at another, the element of danger being the superabundance of fat existing at the time of operation. He further suggests that the storage of superfluous fat may be due, in some cases, to the large quantity of cod-liver oil and fattening diet supplied to delicate, crippled, and rickety children, in the hope of strengthening them, coupled with lack of exercise.

All anæsthetics are solvents of fat. The breaking down of such dissolved fats could give rise to excess of fatty acids, and thus to acetonuria. But the matter is not so simple as Guthrie's phrase, 'superabundance of fat,' would imply. Dudley Buxton reminds us that many very fat people have been exposed to long administration of chloroform without any after-effects.

Why should fat in the liver behave so differently to fat in other parts?

Fat in the liver may be obvious as the result of sepsis, broncho-pneumonia, phthisis, rickets, profound anæmias, and phosphorus-poisoning, to mention the most important conditions. But the amount of histologically demonstrable fat is not an accurate criterion of the total fat in an organ. Thus, as Leathes points out, the fat of nerves does not react to staining reagents for fat if they are prevented, by the use of fixing agents, from undergoing the changes which they would otherwise slowly undergo in the presence of osmic acid. But degenerated nerves contain free fats, which can at once be demonstrated by any of the reagents for fat. In the same way, the total amount of fat normally present in the heart, kidneys, or liver does not give the characteristic reactions, or even yield to fatty solvents, while after degeneration it does so readily. Thus it happens that an obviously 'fatty' organ sometimes actually contains less fat than normal.

Again, Rosenfeld has shown that 'fatty infiltration' of the liver may be really due to transference of fat from other parts. The condition may be fairly called one of 'fatty congestion.' Phosphorus, or diphtheria toxin, seems to act similarly by retarding the normal reaction of the cells, probably by inhibiting the oxidases. The liver normally appears to receive saturated fats, which it converts into unsaturated fats, thereby enabling their final oxidation to be carried

out more easily. If it be unable to do this, fatty infiltration of the organ must occur.

The poisoned liver appears to be unable to oxidize proteins properly, and fats hardly at all. Therefore, as soon as the cells have used up their scanty store of carbohydrate, their starving condition causes a breaking down of tissue protein and a transference of fat to them; yet the fat on arrival there is useless. This transport of fat may be prevented by feeding with dextrose, which will prevent starvation of the damaged liver.

The moral of all this is that more is implied in the term 'fatty liver' than 'fatty accumulation,' which, indeed, may not occur at all. It implies that the vital reactions of the liver have been so altered that it can deal neither with its own fat, nor with the fat reaching it from elsewhere. Its own fat is now present in simple forms, which can be readily dissolved. The conclusion to which we are led is that, while anæsthetics may cause acetonuria as a result of excessive katabolism of fat in any part of the body, they will not cause toxic symptoms, unless the liver is thrown out of gear at the same time, perhaps by inhibition of the oxidases. A diseased liver will naturally be more easily affected than a sound one. A liver which is not only diseased, but shows this by holding its fat in a simple soluble form, will be specially liable to post-anæsthetic poisoning.

III.—Treatment of Acid Intoxication.

The indications for treatment are :

1. To prevent the further formation of these bodies so far as possible. Broadly speaking, this will be accomplished by diminishing the fat in the food, and by administering carbohydrates.

2. To break the vicious circle in autolysis, and combat acid intoxication by neutralizing the acids already formed, or by supplying the deficient bases.

By what methods can we put these indications into practice?

(a) *In diabetes*, it is no use pouring in carbohydrates which cannot be utilized. The difficulty has arisen from the failure to metabolize carbohydrate; but this failure is seldom absolute.

Lævulose was formerly recommended, since it can sometimes be metabolized up to 50 or 100 grammes a day when dextrose cannot be dealt with at all. But this is merely temporary; after two to five days it has no such effect, having been converted by the liver into dextrose. Von Noorden maintains that oatmeal gruel is tolerated when other forms of carbohydrates are not. I have found that, in some cases, this is so for a time, though the sugar has subsequently returned. But his additional suggestion, to give a considerable quantity of butter with the oatmeal, does not appeal to me, in view of the probable origin of these abnormal acids from fat. In order to neutralize these acids, alkalies should be given with a free hand

whenever the ferric chloride reaction appears in the urine, until the urine becomes distinctly alkaline. I have usually given citrate of potash as well as bicarbonate of soda, because it is not neutralized by the gastric juice, and it becomes bicarbonate in the blood, which is where the alkali is most needed. It can be given in 45-grain doses, and is particularly suitable in those milder cases of diabetic acetonuria in which some drowsiness and 'bilious' symptoms are present.

But we know now that the advantage of citrates does not end here, since citric acid appears to have a marked effect in diminishing the production of acetone bodies by enabling the metabolism of fat to follow its normal course.

It is not sufficient to supply the body with bicarbonate of soda, as is generally done; the importance of other bases should be remembered, especially as in diabetes there is a drain on the calcium and magnesium.

A mixture such as this—

Sodii bicarb.	℥i.
Pot. citrat.	gr. xxx.
Calcii carbonatis	gr. iii.
Magnesii carbonatis	gr. iii.
Aq.	ad ℥i.

Tertius horis.

would be of more service.

If, in spite of this, coma supervenes, at least a pint of alkaline solution should be infused intravenously. It is customary to use 2 per cent. of bicarbonate of

soda in normal salt solution, but for the reasons just given it would be better to give other bases besides sodium.* Infusion may lead to a return of consciousness, but unfortunately coma soon reasserts itself. Nor is this surprising, for at present we cannot strike at the root of the mischief, and stop the autolytic ferments. But there are obvious advantages in even such a temporary rally, in which the reason and the powers of recognition are restored.

The general rule is that the total amount of alkali should not be more than about 1 ounce a day. Beyond this amount it is thought to have a depressant action on the heart.

In a condition which, on theoretical grounds, we believe to be associated with deficient oxidation, to which the characteristic air hunger also points, inhalations of oxygen may reasonably be tried. But since the cell lacks oxygen because a link is missing, not much can be expected from them. And when all is said and done, it remains true that, in diabetic coma, 'the duration of life is to be measured by hours rather than days.'

(b) *In the Recurrent Vomiting of Children.*—To ward off attacks, prodromal signs should be noted—white stools, offensive breath, some change in complexion, usually indicative of what are called 'bilious

* In compounding such a mixture it should be remembered that the daily excretion of K_2O is one-half that of the Na_2O , while the excretion of CaO and MgO is each one-twentieth of soda excreted.

attacks,' and the presence of abnormal acids in the urine—then mild aperients and easily digestible foods should be given. Barley-water is usually tolerated. Small doses of grey powder or calomel should be given, also bicarbonate of soda, up to 3 drachms in the day. Normal salt solution *per rectum* is useful. I would suggest that arrowroot might be employed, on the principle that the abnormal acids are checked in their production by the administration of carbohydrates.

(c) *In the Pernicious Vomiting of Pregnancy.*—Whitridge Williams recommends that when the amount of nitrogen in the form of ammonia rises from the normal 3 or 5 to 10 per cent. of the total, labour should be induced. We have already seen, however, that this ammonia coefficient may be a fallacious guide. The condition of puerperal eclampsia differs from this, because the total amount of nitrogen excreted is diminished, and the proportion of ammonia remains constant. But some interesting observations by Longridge suggest that the general line of treatment which I have laid down is applicable here also. He noticed a diminution of alkalinity of the blood in eclampsia, but he did not state whether this was due to the presence of diacetic acid. He gave citrates with the object of bringing up the diminished alkalinity of the blood to normal. As we know, this method is helpful in the acid intoxication of diabetes for a double reason. Another point of interest was that sugar was given by the mouth and rectum, 'in

order to replace the glycogen in the liver, without which that organ could not exert its antitoxic functions.' But a simpler explanation of the beneficial action of carbohydrate is its power of preventing the formation of these abnormal acids. As we shall see in the next section, the sugar may do this by sparing the other food-stuffs in the liver.

(d) *In Post-anaesthetic Poisoning.*—Guthrie suggests as a line of treatment—(1) that before operation on even fat and apparently healthy children careful inquiry should be made as to the history of so-called 'bilious attacks,' which may in reality be those of acidosis. (2) In all cases in which over-fattening and want of exercise are suspected operation should be delayed, if possible, till the patient has been subjected for some days to a fat-free diet. The urine should be examined for diacetic acid, and, if present, a course of alkalies should be prescribed. (3) Both starvation and fright cause acetonuria. He thinks that the four hours' fast for children before operation is too long. He recommends the giving of nutrient enemata, after the lower bowel has been cleared, two hours before and immediately after operation. The effect of fright cannot be altogether controlled, but may be diminished by preventing starvation. Should symptoms of acid intoxication occur despite these precautions, it must be treated as in other cases. Beddard recommends feeding such patients with dextrose by the mouth, or, failing this, by enemata or continuous rectal infusion of a 10 to 20 per cent. solution, or even by infusing

intravenously a 6 per cent. solution. This is based on Rosenfeld's observation that the liver can still metabolize carbohydrate, and therefore fatty congestion is prevented.

Such, then, are in general the lines on which acidosis and acid intoxication must be approached. Though advance has been made, we cannot expect complete success until we have a much clearer conception of the internal metabolism of the cell, a subject on which our knowledge at present is mainly a series of 'guesses and gaps.'

CHAPTER VIII

INTESTINAL INTOXICATIONS

THERE are fashions in pathology, as in dress, and signs are not lacking that intestinal intoxications are coming in for a large share of attention. In the course of a single week lately I heard most of the diseases of hitherto unexplained causation referred to intestinal intoxication. It is such a fatally easy explanation that it is but human to yield to the temptation in face of perplexity.

Englebert Taylor well says that 'the progress of the auto-intoxication theory, like that of every other uncontrolled movement in practical medicine, is like the development of gossip in common life: the first person suggests that it might be so, the second states that it is so.'

Therefore, it is worth while to consider what is really meant by an intestinal intoxication, and what symptoms it might be expected to cause. We can then examine the evidence necessary to establish the fact that intoxication has occurred, and inquire how far that fact is proven in some special cases. It is only in this way that we can get a definite basis for

treatment, though a much more complete conception of the pathology must be reached first. But success lies along that path, while progress will not be made by haphazard reference to pyorrhœa and constipation, important factors though they be.

‘The mucous membrane of the alimentary canal is pre-eminently an absorbent surface—it is constantly bathed in liquids swarming with bacteria.’ The flora is both varied and extensive, yet how seldom does infection by pathogenic organisms or intoxication by saprophytes occur.

Probably microbes constantly invade the body from the alimentary canal, but are as constantly destroyed. Flexner’s studies have shown how commonly a terminal infection occurs when the vital forces of the body are exhausted. Metchnikoff compares the leucocytosis of digestion to the leucocytosis that accompanies reaction to infection, believing the former to be due to the same cause—namely, the resistance of the body to invasion. This must remain doubtful until the rôle of phagocytosis in immunity is more definitely understood; but the comparison is suggestive. At any rate, it would appear that the body possesses two lines of defence against intestinal intoxications and infections, one bactericidal, in the blood; the other antitoxic, in the liver.

Gastro-intestinal intoxication may conceivably occur from—

1. Inorganic poisons—*e.g.*, lead.
2. Organic poisons—*e.g.*, cyanides.

3. Intermediate products of digestion—*e.g.*, peptones, purins.

4. Products of putrefaction—*e.g.*, indol.

5. Products of abnormal pathogenic bacteria present in the intestine.

The first two do not really concern us here. The reaction of the body against them differs in an important particular from the method adopted against bacterial poisons. The neutralizing substances are normally present in the body and are not specific, each of them combining with several poisons. Fromm points out that these reactions are few and simple, such as oxidation, reduction, hydration, dehydration, and methylation. The protective substances are also few, such as proteins, bile acids, glycuronic acid, etc. They are not the result of any special adaptation to meet a pathological condition. They are there as the result of normal metabolism; they have an affinity for various chemical substances, some of which happen to be poisons. If these enter the body, they are neutralized to some extent, though, as a rule, very incompletely. All this is very different from the highly specific nature of the immune substances produced against bacteria and their products.

Intoxication by Intermediate Products of Digestion.

We recognise now that peptone is not the end-product of digestion, but that the process is carried further to simpler amino bodies. As intravenous injections of proteoses and peptones will cause toxic

symptoms, it has been suggested that intestinal intoxications may result from absorption of these intermediate products, the toxic effect decreasing with the decreased size of the molecule. But there is no definite evidence that such an absorption occurs. The most striking example of one of these intermediate bodies appearing in the urine is the albumosuria which accompanies multiple myeloid growths; and here the source of the albumose is almost certainly the growth itself, and not absorption from the intestines.

Passing from the simple to the compound proteins, nucleo-proteins are credited with a toxic power on account of the purin bodies that they contain; but, normally, the liver has the power of destroying these to a large extent.

The importance of the distoxicating action of the liver is readily established. Dogs in which an Eck's fistula—i.e., a communication between the inferior vena cava and the portal vein—has been made showed toxic symptoms, especially after a meal of meat. In fact, the dogs came to recognise this effect of meat, and avoided it, living on foods which contained very little protein.

These experiments show that even in normal digestion the absorbed products are not sufficiently elaborated to be used by the tissues. A further step has to be taken by the liver, and this is one of the most important functions of that organ in metabolism. It is very difficult, if not impossible, to distinguish in all cases between the part played by the liver and the

intestinal mucosa in the distoxication of the food, which is an essential preliminary to assimilation by the tissues. But when in a disease we find an intermediate product of normal metabolism excreted in the urine, I think we must conclude that hepatic insufficiency rather than intestinal intoxication is the cause of the toxic effects observed. For the evidence of the toxic effects of such products is, to say the least, very doubtful.

Intoxication by Products of Putrefaction.

Now, in putrefaction, abnormal products of disintegration may be set free, and we must inquire into their responsibility for symptoms. The great seat of putrefactive change is the large intestine. Proteins putrefy, carbohydrates ferment, and to a certain extent these two processes are antagonistic. Fermentation may be useful to animals that eat a large quantity of uncooked vegetables, because the cellulose resists the ordinary digestive juices, so that until the cell walls are dissolved by bacterial agency the contained food-stuffs are not available. This, however, is not of much use in human beings; but fermentation plays another useful part in antagonizing putrefaction, which may lead to the development of more toxic substances. This is the disadvantage of a large intestine, the advantage being that, by the absorption of water there, the bulk of the fæces is greatly reduced, so that the emptying of the bowel need not occur normally more than once a day. According to

Metchnikoff, the disadvantages outweigh the advantages, and it is hardly too much to say that he looks upon old age as the result of chronic intoxication from the large bowel. The animals with a short colon are long-lived is, in effect, his conclusion; and it seems to be the opinion of some surgeons that it is better for a man to dispense with the services of his colon than to possess an indolent one. This represents the extreme view; yet we can hardly suppose that the colon would have appeared in evolution without a compensatory protective mechanism against such ill results. Bearing this in mind, it will not surprise us to find that the evidence of intoxication by the products of the ordinary putrefactive changes occurring in the intestine is quite inconclusive. Let us see what these changes are, and how far any of the resultant bodies can be incriminated.

As proteins undergo the most changes in putrefaction, let us deal with them first. Whatever the protein, it contains the same four groups, however different the representatives of those groups may be.

Mon-amino Fatty Acids— <i>e.g.</i> , Leucin.	Hexone Bases— <i>e.g.</i> , Arginine.	Aromatic Bodies— <i>e.g.</i> , Tyrosin, Tryptophan.	S
			SO ₂

Putrefaction would seem mainly to affect the right-hand groups in this diagrammatic scheme—*i.e.*, the aromatic bodies and the sulphur groups. Tyrosin

yields phenol compounds, while tryptophan yields indol and skatol; the oxidized sulphur appears as sulphates, and the unoxidized as sulphides.

‘Intoxication with sulphuretted hydrogen certainly but rarely occurs’ (Taylor). As we shall see, sulphur may form a compound with hæmoglobin with toxic results. The sulphates conjugate with the aromatic products to form ethereal sulphates, which are practically harmless. Such of these ethereal sulphates as are reabsorbed appear in the urine. Indican is one of these, being indoxyl-sulphate of potash. As this is readily detected in the urine because of its striking colour reaction, much of the theory of intoxication by putrefaction centres around this substance.

The tests usually employed are—

1. To 2 inches of urine in a test-tube add 1 inch of strong HCl and 5 drops of fuming HNO_3 ; boil; allow to cool; add $\frac{1}{2}$ inch of CHCl_3 , and shake up thoroughly. If indican be present, the CHCl_3 , when it has again sunk to the bottom, will be tinged blue or red.

2. Obermayer’s reagent (strong HCl, specific gravity 1.19, and 4 grammes ferric chloride per litre) gives a red colour in the presence of indican.

But we cannot conclude, from simply getting this striking reaction, that we are dealing with a case of intestinal intoxication. In the first place, ‘constant relationship between putrefaction and intoxication could only hold if the aromatic bodies were themselves toxic, or if the pairing were a tax on the body.’

But, even if it were so, we cannot judge of the total paired sulphates from the amount of indicanuria alone, which only represents one of them. The time given for reabsorption will also be greatly influenced by the rate at which the contents are passing along the canal. Bearing all this in mind, it is almost idle to expect to diagnose an intoxication from this reaction alone. Herter obtained a marked indican reaction in the following varied series of cases: three cases of epilepsy, two of muscular rheumatism, and one each of myxœdema, acute intestinal obstruction, pseudo-hypertrophic paralysis, urticaria, leukæmia, tetany, arthritis deformans, and chronic nephritis. It would be a bold man who would seek a common cause for all these conditions!

He found also that, even after injecting as much as $\frac{1}{2}$ gramme of indol into the femoral vein of a dog, he was unable to detect any indol in its blood, showing that the body has the power of rapidly transforming considerable amounts.

Administration of indol in repeated doses to rabbits caused loss of weight, among other symptoms. In man, the administration of considerable amounts caused headache and other uncomfortable sensations in the head, with indisposition for mental or physical exertion. He suggests that this latter condition, if prolonged, may perhaps form the basis of a neurasthenic state. In thirty-two cases of neurasthenia he obtained a marked reaction for indican twenty-one times, a slight or no reaction eleven times. He concludes

that, while indol is not an indifferent substance, we cannot regard it as ordinarily exerting highly toxic effects, even when absorbed in unusually large amounts. This is what we might expect, *a priori*, in the case of a normal decomposition product of protein food.

I would suggest that whether such substances do or do not exert their toxic effect depends largely on whether they are free, or whether there is sufficient sulphate for them to combine with, in which state they are harmless. In support of this idea, I may refer to a striking case recently described by A. E. Garrod. He examined the urine of a woman who for many years had applied a dressing of carbolic oil (1 in 20) to an ulcer on the leg. He reported that she was on the verge of carboluria, although the urine did not darken at all on standing. This statement was put to the test, for the carbolic dressings were resumed, with the result that the patient did have an attack of carboluria! Garrod's opinion was based on the observation that almost all the sulphates were in the form of ethereal sulphates—*i.e.*, her power of neutralizing the toxic effects of phenol was taxed almost to the full. A little more and she was over the brink.

Now, indol is closely related to phenol chemically; and the case suggests two considerations: (1) When we test for indican, we are testing for just that part of the indol which has been rendered inert. (2) We here have an explanation of the comparative

failure of the phenol compounds as intestinal antiseptics. By combining with the sulphates they deprive the body of the power of rendering harmless those putrefactive substances of which they cannot altogether prevent the formation.

In fact, the ratio $\frac{\text{ethereal sulphates}}{\text{simple sulphates}}$ gives us a much surer indication of the existence or approach of an intoxication by aromatic bodies than we can possibly obtain by testing for indican.

The other two food-stuffs may be held almost guiltless as a cause of intestinal intoxication. In fermentative dyspepsia carbohydrates may give rise to oxalic acid, causing oxaluria; more commonly they are a source of lactic acid, which is antagonistic to putrefaction. Fats will produce fatty acids as a result of bacterial action, but these will not produce toxic symptoms. The fatty acids associated with acid intoxication in diabetes, for instance, are formed in the tissues, not absorbed from the intestine.

The case for the occurrence of an intoxication from the bowel by the normal or ordinary putrefactive products of food-digestion cannot be regarded as proven. Yet on this unstable foundation the most airy and far-reaching hypotheses have been reared. Forcheimer, for example, draws the following conclusions from seventy-seven cases which he had diagnosed as intestinal intoxication, but the clinical picture presented does not seem to have any definite or consistent features; In the gastro-intestinal tract there might

be pyorrhœa alveolaris, various forms of stomach troubles, changes in the functional activity of the colon, and demonstrable retention of fæces. In a large percentage of the cases indican was increased in the urine, while half the cases showed calcium oxalate crystals, uric acid, and urates. In about one-third of the cases red corpuscles were found in the urine, and in about the same proportion polyuria alternated with oliguria. Half the female cases had menstrual trouble. Nervous symptoms were very common, thirty-one out of the seventy-seven cases having headache. In fifty-eight cardio-vascular changes were observed, over one-half of these being due to neuroses and myocardial conditions. Fifty had symptoms in the motor apparatus, such as gouty joints, and especially muscular symptoms; twenty-two had skin lesions.

All this is much too vague to afford us any idea as to what constitutes an intestinal intoxication, and by what signs we shall recognise it. Opinion at present may be favourable to the view that many lesions of the joints, muscles, and skin are due to this cause, but we still lack tangible evidence.

From these rather nebulous ideas let us turn to some instances in which the evidence for an intestinal intoxication is more concrete and definite. These are all examples of—

**Intoxication by the Products of Apparently Pathogenic
Bacteria present in the Intestine.**

Wells suggests two explanations of their occurrence :

1. The intestinal flora become altered because of the changed conditions, and bacteria thrive that produce specific toxic substances.

2. Many unidentified poisonous substances are produced in the alimentary canal which ordinarily are destroyed, but under certain conditions are reabsorbed.

At present, those cases which have been most clearly worked out seem to fall under the first head. In many instances it will be difficult, if not impossible, to draw a hard-and-fast line between intoxications and infections, because we cannot tell whether the microbe has been able to enter the portal bloodstream and has become bacteriolized there, or whether the intestine has merely absorbed the toxins produced in the intestine. Indeed, we can sometimes recognise three stages in the same case :

1. Intestinal absorption of toxins only.

2. The organism in the portal blood, soluble toxins in the general circulation.

3. The organism in the general circulation—*i.e.*, septicæmia.

As an example of a disease that may be either an intoxication or an infection, we may take Hamilton's work on 'Louping-ill,' or paralytic chorea in sheep,

because it gives us a clue as to the line along which research will have to be carried out in man to establish the pathology of like conditions. Louping-ill is a terribly fatal disease affecting sheep on the west coast of Scotland between the months of April and June. There are three stages of the disease :

1. The animal is apathetic, and staggers as it walks;
2. Spasmodic convulsions occur, which may go on to coma or to—
3. Flaccidity, with abolition of reflexes.

Sometimes there is diarrhoea with passage of blood. Recovery seldom, if ever, occurs. There are two kinds of cases : in one there is excess of turbid and sometimes blood-stained peritoneal fluid, while in the second there is probably no excess and the fluid is clear.

The turbid fluid contains a large, coarse-looking rod organism, with a great tendency to spore ; the clear fluid showed the same organism on incubation in sealed tubes for twenty-four hours.

Injection of liquids containing spores reproduces the disease, and the same organism can be obtained from the contents of the bowel. It is present in enormous numbers in the secretion on the surface of the intestinal mucosa. The intestine seems to be the portal of entrance. When the organism is injected subcutaneously, death takes place from acute toxic poisoning before the characteristic nervous symptoms

can develop; when introduced by the alimentary canal, these are well developed.

The cause of the periodicity of the disease appears to be that the blood is bacteriolytic to the organism at other seasons. May not similar periodicity occur in man in certain diseases? For instance, attention has been drawn to the great liability to infective endocarditis during the fall of the leaf, and the frequency with which some intestinal streptococcus is found responsible in such cases.

He bacteriolized the organism by the blood of sheep *in vitro*, filtered, and injected the filtrate subcutaneously, causing the characteristic symptoms. Thus an intoxication may occur, even though an infection has been prevented by the destruction of the microbe.

Immunity may be conferred by feeding an animal on cultures during the period of the year that it is insusceptible, which recalls the immunity acquired to typhoid fever by the inhabitants of a district in which it is endemic.

As he suggests, probably dead cultures would do as well. The administration of vaccines by the mouth with saline or serum is a development along these lines.

I should like to emphasize the fundamental importance of these experiments, in which the method of infection is clearly worked out, and the line of successful treatment clearly laid down.

: Horder (*St. Bart.'s Hosp. Journ.*, February, 1908) records a striking example of the way in which the

method of infection can be worked out in human beings. A boy, aged seven, had been playing in a field where the contents of a house privy were being deposited. The next day he vomited and complained of abdominal pain. The temperature was of an intermittent type, the stools contained mucus and blood, and he became jaundiced. On the twenty-sixth day the elder brother, aged twelve, was seized by an illness which began to run the same course. Cultures from the blood and urine were sterile. Cultures from the faeces were plated out, and agglutination tests were undertaken with the blood of both boys against the dominant strain of colon bacillus present in the faeces; clumping occurred readily. The conclusion was that the most probable cause of the portal infection was a virulent colon bacillus. It will be noted that, as far as the general circulation was concerned, only a stage of intoxication had been reached, since the blood was sterile. A vaccine was prepared from this bacillus, and two doses given to each boy, with an interval of five days between the doses. Rapid improvement followed, although the cases were at different stages of their illness, so that the recovery could not be explained as the natural termination of the attack.

Another case recorded by him was hardly less striking—a man suffering from rapid emaciation and periodic bouts of fever. There were no physical signs in the chest, and no tubercle bacilli were found. *Pyorrhœa alveolaris* was present to a marked degree.

A tooth was extracted, and a culture made from the fang. A streptococcus was isolated, giving the reactions of the salivary type. A vaccine was prepared, and injected twice. All symptoms ceased after the second injection. The blood was sterile. I particularly refer to this case, as I have deprecated indiscriminate reference to pyorrhœa as an explanation of diseases of obscure causation; this is the very antithesis of such methods, the proof of intoxication from this cause being complete.

Microbic Cyanosis.

Five years ago Stokvis described cyanosis as a result of intestinal troubles. The abnormal colour was due to the presence of methæmoglobin in the red corpuscles. The patient had great intestinal irritation, clubbing of the fingers, deep cyanosis, and considerable albuminuria. After death it was discovered that he had suffered from parenchymatous nephritis, with ulcerative enteritis. Talma had three such cases, and he was able to find a large amount of indol in the urine.

Van der Bergh found the connecting-link between the intestinal trouble and the resulting blood changes to lie in the presence of nitrites, which are well known to lead to the formation of methæmoglobin. He found that the condition would clear up in from twenty-four to forty-eight hours on a milk diet, but returned in four hours after an ordinary meal. He also described four cases of sulphæmoglobin anæmia—

i.e., a sulphur compound of hæmoglobin, which would additionally suggest an intestinal source for the intoxication.

Gibson described a case in a married lady, aged thirty-six, who had been cyanosed for two or three years. The face and hands were of a lavender hue, while the lips, ears, and nails were nearly as dark as bilberries. The spectroscope showed the band of methæmoglobin, while nitrites could be detected in the blood, fæces, and saliva. An organism, either the *B. coli communis* or a very closely allied form, was isolated from the blood at one examination.

As the result of a careful and assiduous intestinal antiseptis, a great improvement had occurred. No trace of methæmoglobin could be found, nor could any coliform organism be detected in the blood. He suggests that in those cases where recovery does not follow intestinal antiseptis the colon should be washed out by an opening into the cæcum.

Lately, I had the opportunity of seeing the first case of sulphæmoglobinæmia recognised in this country, which was under the care of Dr. Samuel West at St. Bartholomew's Hospital.

An unmarried woman, aged thirty-seven, was admitted for debility and cyanosis. The skin was of a leaden hue, resembling that of silver staining. The colour was due to the blood, and not to deposited pigment, for on pressure the skin could be shown, when emptied of blood, to be of the normal hue. The fingers were not clubbed. I examined the blood

spectroscopically in the circulation by holding the patient's hand in front of an electric light and pressing the web of the thumb between two glass slides until a convenient thickness was obtained. A spectrum closely similar to that of methæmoglobin was obtained, with a well-marked band in the red. I was at that time ignorant of Van der Bergh's work, and everyone regarded the case as one of methæmoglobinæmia. Drug habits were therefore suspected. These, however, could be excluded with an unusual degree of assurance. The medical man who had attended her stated that, except for occasional doses of bromide and iodide, he had given nothing more for a long time than a tonic of iron with arsenic. The patient lived in a remote part of the country, from which the nearest druggist's shop was some miles away; she could only have got drugs by post. But neither her family or the postman knew anything of her receiving such parcels. Moreover, during her stay in the hospital she certainly had no such drugs, and yet the cyanosis persisted.

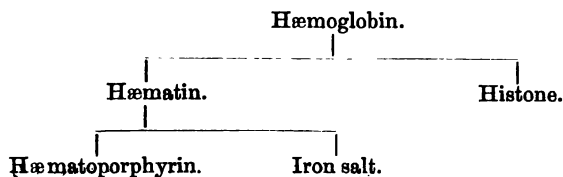
A more thorough examination of the blood by Wood Clarke revealed the fact that the bands were those of sulphæmoglobin. The urine contained less indol than usual—an interesting comment on the slight value to be attached to this body as evidence of an intestinal intoxication. The ethereal sulphates were greatly reduced. Nitrites were found in the urine. No increase in sulphuretted-hydrogen-forming organisms could be found in the intestine. A culture

taken from the blood in the arm was sterile. Moreover, the long duration of the case was against the theory of an infection, and pointed rather to an intoxication.

West says: 'It is possible that the cause may lie in the intestinal walls rather than in their contents, and that the error may be a hyperabsorption rather than a hyperformation,' and, if so, it is of all the more interest as an example of what I have stated to be very rare—*i.e.*, an intoxication by a substance formed in the ordinary processes of intestinal putrefaction.

'Contrasting the two groups, it would appear that the methæmoglobin cases were associated with diarrhœa and improved greatly on a milk diet, while the sulphæmoglobin cases were associated with constipation, and did not improve until this was relieved.' This case improved greatly on systematic treatment by aperients.

It may be desirable to say a few words about another toxic alteration in the hæmoglobin molecule. This is the condition in which it is broken down into its constituent groups, so that one of its end-products, hæmatoporphyrin, appears in the urine. The decomposition of the hæmoglobin molecule may be tabulated as follows:



A trace of hæmatoporphyrin is a normal constituent of urine, but under certain conditions this is largely increased in amount. For some years this has been known to occur in sulphonal poisoning. Trional and tetronal are also capable of producing it. But there is another group of cases where such drugs can be excluded. When not occurring as a train of toxic symptoms, this has no specially unfavourable significance, though it must denote a profound disturbance of pigment metabolism.

Occasionally, however, toxic symptoms, such as vomiting, thirst, anorexia, abdominal pain, and profound prostration, occur with the hæmatoporphyrinuria. Ranking and Pardington described two such cases, and I have recently had one under my care in which three attacks of this character had led to the suspicion of intestinal obstruction. McCall Anderson met with the combination of hydroa æstivalis with hæmatoporphyrinuria in two brothers. Monro has seen hæmatoporphyrinuria in periodic vomiting with acetonuria in a boy.

All these points are suspicious of an intestinal intoxication, and the suspicion is strengthened when we remember that hæmoglobin will break down into hæmatoporphyrin much more readily in the reduced state than when containing oxygen. Now, Hurtley and Wood Clarke have shown that in the formation of sulphæmoglobin the blood pigment is first reduced, and then combines with the sulphur.

This suggests that in both cases some reducing agent

is at work, and the intestinal symptoms point to the alimentary canal as its source. It is interesting to compare this condition with methæmoglobinæmia, which has been proved to result either from intestinal intoxication or from coal-tar drugs.

In the future many other conditions may be proved to be due to intestinal intoxication, but the evidence is not at present convincing. A few of these may be briefly referred to.

Hunter has laid great stress on oral, gastric, and intestinal sepsis as the cause of *pernicious anæmia*. I think we must admit that there is a strong case for hæmolysis in the portal area in these cases. Now, Hamilton finds that the anaerobic bacteria naturally present in the human intestine include some highly pathogenic members which under proper surroundings can produce marked hæmolysis.

Though *cirrhosis of the liver* occurs in alcoholic subjects, it is known that the direct administration of alcohol experimentally leads to a fatty and not to a fibrotic change in that organ. Consequently the condition has been referred to impurities in the common alcoholic drink of the country. Thus in wine-drinking countries the potassium sulphate with which the *vin ordinaire* is plastered, and in whisky-drinking countries the fusel oil, have been held responsible. Such wide differences of opinion make it all the more probable that the ingredient common to them all, the alcohol, is really the agent at work. Rolleston explains this dilemma by the view that alcoholic

excess leads to a prolonged gastric catarrh, which, by lowering resistance, enables toxic substances to be absorbed from the bowel. Hamilton's suggestion, which harmonizes with this quite well, is that a microbe is absorbed from the intestine, bacteriolized in the portal blood, and its liberated toxins anchored on to the liver substance. This might occur in others than alcoholic subjects, and it certainly appears that we cannot explain all cases of multilobular cirrhosis by alcoholism.

There is a growing opinion that *chronic affections of the joints* are due to a chronic infection or intoxication. Rheumatoid arthritis is very much a case in point. Either the alimentary or the genito-urinary tract may be the 'open door' by which the infective agent enters. And so it has come about that pyorrhœa alveolaris has been regarded as a potent cause of the disease.

The Cambridge workers found a history of infection in 20 per cent. of their cases, the most common being influenza. They found defective teeth in more than 50 per cent. ; but, as they rightly say, too much stress cannot be laid on this, as a large proportion of the cases belonged to the lower classes, in which sound teeth are the exception. Indeed, on the methods of collecting statistics only too commonly adopted, I would guarantee to prove that any disease you care to mention was due to defective teeth. Still, I think in this case there is sufficient evidence to make it desirable to pay careful attention to the condition of

the mouth in rheumatoid arthritis, especially as the routine line of treatment can hardly be considered satisfactory. *Tetany* is another condition which has been held to be due to a gastro-intestinal intoxication. Its occurrence in rickets, with gastro-intestinal disturbances, in typhoid fever, and after lavage for dilated stomach, is certainly suggestive.

But I do not wish to multiply the list of diseases in which an intestinal intoxication might conceivably be held responsible. For the present this is mere speculation. We may lay down the following conclusions as to etiology:

1. There is no satisfactory proof of intoxication by the ordinary disintegration products of digestion.

2. Putrefactive processes mainly affect the aromatic—*i.e.*, benzene—groups of the protein molecule; there is no evidence that these can lead to symptoms of intoxication. Occasionally the sulphur in the protein molecule appears to be able to cause chemical changes in the hæmoglobin, with resulting cyanosis. But as sulphur must always be set free in the putrefactive changes ordinarily occurring, we shall probably find that here, too, some abnormal bacterial agent is at work.

3. Careful examination has failed to reveal the presence of ptomaines as the cause of any of these chronic intoxications.

4. It is clear that it is often difficult, if not impossible, to draw a hard-and-fast line between an infection and an intoxication in these cases. Hamilton's re-

searches provide us with an explanation. The microbe may sometimes be able to establish itself in the blood-stream, thereby producing an infection, while sometimes it is rapidly destroyed by the blood, but is, nevertheless, able to disseminate its soluble toxins in sufficient quantity to produce definite symptoms. I believe we shall ultimately be able to refer all the real intestinal intoxications to the presence of actively pathogenic bacteria among the ordinary saprophytes of the intestine.

Treatment.—Clearly the most rational procedure will be to try and isolate the microbe responsible, if possible. If a blood culture be sterile, a plate culture may be made from the stools, and the effect of the patient's blood in agglutinating the more definitely pathogenic organisms tried. If we get a positive reaction with one or more of these, we may conclude that this, or these, as the case may be, can be held responsible. If, further, a vaccine is prepared from such organisms, and its injection benefits the patient, we shall at once have established the fact that the case is really one of an intoxication, and have initiated the rational treatment for it.

I freely admit that at present it is not practicable to work out cases in ordinary practice in this way, but we may look forward with a fair measure of confidence to a time when we shall be able to correlate certain definite signs and symptoms with certain distinctive microbes. This is, at any rate, the line along which advance will be made, and not by casually testing the

urine for indol for diagnosis, and for treatment, purging and extracting all the teeth.

Micro-organisms form one-third of the total solids of the stools. Intestinal antiseptics is a counsel of perfection, and at present we are scarcely prepared to accept Metchnikoff's dictum that senile changes are the result of an intoxication from the large bowel, so that it is hardly likely that we shall attempt to practise intestinal antiseptics as a routine treatment. Occasions have doubtless arisen in the experience of all when it has appeared desirable to do something in that direction, but a sense of despair was felt in trying to accomplish it. Salol cannot be said to have been a success, and I have suggested a physiological reason for its failure. Naphthol, in 5-grain doses in cachets, has given better results. Naphthalene tetrachloride, in 5- or 10-grain doses, has been used with more success. As it is insoluble, and cannot, therefore, be absorbed, it cannot produce a toxic effect. Strasburger has found tanacol, in doses of 40 to 60 grains a day, produce a notable reduction in the intestinal flora. Cohendy has been able to reduce the intestinal microbes to one-thirteenth of their former number by the use of thymol.

Calomel, in small and divided doses, followed by a saline purge the next morning, is, of course, a time-honoured method of attempting to effect intestinal antiseptics. However useful this may be to start treatment, we must beware of a routine use of strong purgatives to this end, for by removing the superficial

epithelium of the bowel they may facilitate septic absorption. And cases of intestinal intoxication leading to methæmoglobinæmia are associated with diarrhœa, so that purgatives would be inadvisable here, except as an initial step.

Metchnikoff has suggested another way of attacking this difficult problem. Instead of attempting to render the bowel aseptic, he advises the introduction of other organisms which are antagonistic to the growth of the putrefactive bacteria. These are the lactic-acid-producing organisms. Soured milk has long been a staple article of diet among Oriental people, and enjoys a high repute as a hygienic measure. James Riley, in 1854, claimed that it had an extraordinary effect in promoting longevity. He asserted that wandering Arabs, subsisting almost entirely on the fresh or soured milk of camels, lived for two or three hundred years! It may be added that Riley was an American.

Belonowsky thought that cultures of *B. lactis*, sterilized at 120° to 140° F., were better than doses of lactic acid, apparently because some other adjuvant substance is produced by the bacillus besides the lactic acid. For similar reasons the addition of the paralactic bacillus has been recommended.

Bulgarian 'yahourth,' or 'yoghourt,' is milk soured by the most powerful lactic-acid-producing bacillus known. Unfortunately, the commercial product in use contains a diplococcus and a strepto-bacillus also. However, preparations of selected lactic ferments are

now on the English market. But some of these preparations tested at St. Bartholomew's Hospital have been found quite inert. Allen and Hanbury's Sauerin was the most active preparation of those tested. One or two tablets are taken three or four times daily after meals, which should include some sugary substance, or the tablets may be used to curdle milk, which is taken in that form.

This line of treatment is quite harmless, and is worth a trial. The extravagant claims that have been made for it in some quarters have, no doubt, excited some degree of prejudice against it.

We may summarize the points of treatment in a case of proved intestinal intoxication as follows :

1. A simple diet in which milk (reinforced with lactic-acid ferments, if you will) plays a large part.
2. Ordinary regulation of the bowels, without any drastic purgation.
3. Naphthalene tetrachloride may be used as an intestinal antiseptic.
4. Attention to septic conditions of the mouth.
5. Identification of the microbe responsible, and preparation of the appropriate vaccine.

CHAPTER IX

IRREGULAR ACTION OF THE HEART

ACCORDING to James Mackenzie, whose admirable studies have contributed so much to our knowledge of the subject, there are three main circumstances which have combined to throw light on irregular action of the heart. These are the experimental discoveries of the nature of the functions of the heart muscle, the application of graphic records of the jugular pulse to the interpretation of heart irregularities, and the discovery of the remains of the primitive cardiac tube in the mammalian heart, with its physiological significance.

Though the origin of the cardiac rhythm has interested physiologists for many years, it has been regarded as outside the sphere of practical medicine until quite lately. In reality there is no reason why this should have been so; probably the interest excited by the auscultation of cardiac murmurs has tended to distract attention from the cardiac rhythm. Yet in treatment our aim is to restore a normal rhythm; we cannot repair a valve.

It is to Gaskell that we owe our fundamental conceptions of cardiac rhythm. Here, as in his pioneer work on the sympathetic nervous system, his philosophical insight enabled him to lay the foundations so well and truly that it has only been left to others to build along his lines. After more than twenty years this work is beginning to be applied to clinical medicine, with excellent results.

Previous to Gaskell, physiologists had referred the rhythm of the heart to the intracardiac ganglia. Bernstein had shown that if the ventricle of the frog's heart were 'physiologically disconnected' by crushing the auriculo-ventricular junction with a fine pair of wire forceps, it remained quiescent, while the rest, which contained ganglion cells, continued to beat. But Gaskell showed that if the intracardiac pressure were raised by ligaturing the aortæ, the ventricle would beat rhythmically once more.

In the tortoise's heart he was able to divide the septal nerve which passes between the two intracardiac ganglia without disturbing the rhythm; and by a series of interdigitating cuts in the auricular substance he compelled the wave of contraction to pass along a zigzag strip of muscle between the sinus venosus and ventricle, though all nerves must have been divided. Finally, by warming the ventricle and cooling the sinus, he was able to alter the relative excitability of the two ends of the heart so much that a reversed rhythm was produced. His conclusion was that rhythm was an inherent property of the

cardiac muscle, and did not depend on the intracardiac ganglia. The beat normally began at the sinus, because here the muscle was of a more embryonic character, while the ventricular muscle was the most differentiated.

He went on to show a point which has now become of great practical importance. If the bridge of auricular muscle be made too narrow by cutting, a 'block' is established on the course of the muscle wave, so that not every beat can pass over into the ventricle, but only alternate waves, or one out of every three, according to the width of the bridge. But after inhibiting the heart by stimulation of the vagus, the muscle accumulates enough energy during the enforced rest to enable it to convey every beat across the narrow bridge. On the other hand, in the period of comparative exhaustion following sympathetic stimulation, the conductivity is lowered, so that fewer beats can pass over. An adequate strand of conducting tissue is essential to the due propagation of the wave of contraction along the cardiac tube.

Before these results could be applied to the mammalian heart it was necessary to prove the existence of muscular continuity between auricle and ventricle, which at that time was not thought to be present. Stanley Kent was the first to do this, in 1893; but His, and then Tawara, worked out the nature of the connecting band or 'auriculo-ventricular bundle,' as it is now called, in much greater detail.

It begins near the anterior edge of the right coronary vein, and then passes forward on the right side of the auricular septum below the foramen ovale. Just below the insertion of the median flap of the tricuspid valve this bundle forms a knot-like thickening, the auriculo-ventricular node or *Knoten*, produced by a confused mass of muscle fibres. From this knot a process arises which penetrates the fibrous septum and runs along just below the pars membranacea of the septum, dividing into two main branches, which pass obliquely downwards, one on either side of the septum under the endocardium. So far these fibres do not blend with those of the ordinary cardiac muscle, being enclosed in a separate fibrous sheath; but when they reach the papillary muscles they divide into a large number of branches, some of which enter the papillary muscles, while others pass on beyond them and follow the course of the small trabeculae to the parietal wall, where they branch upwards and downwards under the endocardium lining the whole inner surface of the cavity of the ventricle, to fuse everywhere with the ordinary cardiac muscle fibres.

The heart muscle of elderly people being of a brownish colour, the left main branch, with its two secondary branches, stands out very plainly on account of its rather greyish-white colour, but it can be recognised with practice even in the hearts of younger individuals. The node is made up of fine, pale, thin, branching fibres with faint striation, which

in some respects resemble embryonic muscle fibres. The fibres interlace and fuse with one another, thus contrasting with the elongated parallel arrangement of the rest of the cardiac muscle. The branches and terminal filaments of the bundle resemble the fibres, described in 1845 by Purkinje, in the subendocardial layers of the sheep's ventricle. Morphologically and histologically these fibres represent the invaginated portion of the primitive tube from which the complex heart of the mammal is built up.

But if these primitive fibres are the conducting strand along which the wave of cardiac contraction passes, we should expect to find them at the junction of the great veins with the heart, for this is where the wave starts. Recently Keith and Flack have found a remnant of primitive fibres persisting at the sino-auricular junction, which are in close connection with the vagus and sympathetic nerves, and have a special arterial supply. This is called the 'sino-auricular node.' Here the dominating rhythm of the heart may be believed to arise normally, and here it may readily be modified by those extrinsic nerves which are known to be able to influence it.

The anatomical evidence is therefore amply in favour of extending Gaskell's conceptions to the mammalian heart. And Hering was able to produce a complete stoppage of the supraventricular parts of the heart by a cut made at the sino-auricular junction; while Erlanger has shown experimentally that it is possible, by interfering with the auriculo-

ventricular bundle, to reproduce the phenomena described by Gaskell in the tortoise's heart, and many of the forms of irregularity met with clinically. A clamp was devised in which a small piece of tissue, including the bundle, could be subjected to varying degrees of compression while preserving its normal relations. With very slight compression there was merely a lengthening of the normal pause between the auricular and ventricular contractions. These intersystolic periods, however, usually lengthen, until eventually the ventricles fail to respond to one of the excitation waves. In the next cycle the intersystolic period, owing very probably to the increased excitability of the rested ventricular muscle, is unusually brief. In succeeding cycles it again progressively lengthens until the ventricles again fail to contract.

Upon further tightening, further stages of heart-block occur, the auricles giving three or four beats to each ventricular contraction. When the efficient excitation waves from the auricles occur at longer intervals, the ventricles begin to beat independently. Thus a complete dissociation of the auricular and ventricular rhythm results.

Before discussing the clinical equivalents of these phenomena, it will be well to consider a little more closely the physiological peculiarities of cardiac muscle.

For it might be urged that we have merely said that the heart beats because of its inherent rhythm, an explanation worthy of mediæval schoolmen. But

the intention at that stage was merely to distinguish between the parts played by muscle cell and ganglion cell respectively, without attempting to explain them. The following facts throw some light on this rhythmical power :

1. If a resting cardiac muscle be stimulated by a series of shocks, a progressive improvement is seen in the first few beats, producing the so-called *staircase*. Each beat acts as a stimulus to the next, so that a rhythm, once started, will tend to be maintained. This is apparently due to the stimulating effect of the carbon dioxide produced by the muscle. It is very interesting to note that carbon dioxide is a stimulant both to the heart and the respiratory centre, for in this way it provides for its own removal.

2. *All shocks are maximal* to the cardiac muscle—that is to say, whether a large or small shock be given, the response is the same, the muscle giving the best beat it is capable of at that moment. This is not a contradiction of the previous statement ; the staircase would be seen just the same whether large or small shocks, or shocks of varying strength, were used. As long as the stimulus is effective the muscle gives the same response to each.

3. Cardiac muscle has a *long refractory period*. If a shock be sent in just after a beat has begun, the stimulus is ignored ; if it be sent in a little later, a small beat is given after the ordinary one ; but the heart makes up for this by a longer pause, so that the

third beat does not start till the usual time. It is therefore impossible to throw heart muscle into tetanus.

These facts can be partly explained on the analogy of a gun. When the gun is loaded, it does not matter whether much or little force is expended in the pulling of the trigger, the whole charge is fired off; and when the charge has been fired off, it does not matter how forcibly the trigger is pulled, there is no response. The analogy fails in that we are able to get a small contraction when the fibre has partly recharged itself. All this points to an elaboration of contractile material in the muscle substance, which is 'fired off' as soon as enough is accumulated. Normally the charge is fired off by the train laid in the auriculo-ventricular bundle.

We do not know at present what the charge is composed of, but we do know that ionized salts play a large part in its elaboration. For whereas dialyzed serum will not maintain cardiac rhythm, a saline fluid, such as Ringer's, which contains salts of sodium, potassium, and calcium, is highly efficient for this purpose. If the potassium be omitted the heart does not relax properly, while if the calcium be left out systole becomes imperfect. And Locke has shown that the addition of dextrose and oxygen to Ringer's fluid makes it a remarkably efficient medium for maintaining rhythmical contractions in an excised heart. In the presence of these substances, then, the heart is able to keep up a supply of its contractile material.

This is not really incompatible with Carlson's ideas. According to him, the peculiarities of cardiac contractions are due to the heart wall being an intimate blend of muscle and nerve. His conclusions were reached by studying the contractions of the heart of *Limulus*, or king-crab. Here the muscular and nervous elements are anatomically separable, and the muscle is found to approximate in its reactions to those of ordinary muscle. And Rohde found that if he perfused chloral hydrate through the mammalian heart, a stage was reached at which the heart responded to direct stimulation like ordinary muscle. It is readily tetanized, the characteristic refractory period is not in evidence, and the heart responds to stimuli of gradually increasing strength with contractions of gradually increasing amplitude. His interpretation is that chloral has accomplished pharmacologically the severance of the nervous and muscular elements, which can be performed anatomically in *Limulus*. If we regard the cardiac wall as neuromuscular in structure, it does not dispose of the argument that the rhythm is independent of the macroscopic ganglia, but is conducted along a strand of embryonic fibres, which represent the remains of the old primitive cardiac tube.

This strand of tissue must represent more than a mere conducting bundle, however. Keith found in a case of heart-block of eighteen years' standing that the bundle below the site of destruction was quite healthy. If it were merely a conducting bundle, it must have

atrophied. As it did not, it must have some other function; it must be able to create as well as to conduct a stimulus.

Types of Disturbed Cardiac Rhythm.

1. **Heart-Block.**—*Every auricular contraction is not followed by a ventricular contraction.*

The significance of the physiological data was first recognised in clinical work in connection with the very gross interference with the normal rhythm which occurs in Stokes-Adams disease. Though described by Robert Adams of Dublin as long ago as 1827, and again more fully by Stokes in 1846, it has only attracted general attention during the last decade. Osler defines the features of the disease thus :

(a) Slow pulse, usually permanent, but sometimes paroxysmal, falling to 40, 20, or even 6 per minute.

(b) Cerebral attacks, vertigo of a transient character, syncope, pseudo-apoplectiform attacks or epileptiform seizures.

(c) Visible auricular impulses in the veins of the neck.

Huchard regarded the condition as due to atheroma or other organic changes in the bulbar arteries, causing the fits and leading to inhibition of the heart through vagal stimulation. Apart from the fact that careful examination of these arteries may reveal no alteration in them, there is a fatal objection to Huchard's interpretation. The vagus acts mainly, if not solely, on

the auricles. Now, in Stokes-Adams disease the auricular rhythm is usually normal, while the ventricles beat very slowly, and for a time may cease their contractions altogether. This strongly suggests that the main difficulty is due to defective conduction between auricles and ventricles, the cerebral symptoms being secondary, and produced by anæmia of the brain. The only objection to this view is that there is not an entire agreement between the degree of heart-block and the occurrence of the fits. The vagus, no doubt, can play a part in this way; the first effect of vagal stimulation is to depress conductivity, though it subsequently improves it. A heart in which conductivity is already depressed is unduly sensitive to ordinary vagal stimulation; thus a patient of Mackenzie's could bring on cardiac irregularity simply by the act of swallowing.

But the real cause of the disease is seen clearly when we examine the anatomical changes found in cases of the Stokes-Adams syndrome. The following are some of the principal changes that have been found: gummata (Handford, Keith and Miller); anæmic necrosis consequent on thrombosis of the nutrient arteries (Jellick, Cooper, and Ophuls); fibrosis (Barr, who, however, does not admit the significance of this; Schmoll, G. A. Gibson, A. G. Gibson); new growth (Sendler, Luce); atheroma (Stengel, Aschoff); fatty infiltration (Aschoff). That similar symptoms can be produced by pathological conditions so diverse supports the idea that the one feature

common to them all—*i.e.*, interference with the conducting bundle—is the essential cause.

The following case, recently under my care, exemplifies the clinical features of this disease. A Jew, aged thirty-nine, was admitted to the Metropolitan Hospital, with the history that he had been in his usual health until fourteen weeks before, when he began to suffer from numbness of the extremities and headache. He was easily fatigued on the slightest exertion. He was well nourished, and of a good colour. His chest was emphysematous, so that the apex-beat could not be seen or felt, and the area of cardiac dulness was diminished. The sounds were soft, but there was no murmur. His pulse was 80, and regular; the systolic pressure was 120 millimetres. The urine was free from albumen. Three days later he complained of epigastric pain and tightness across the chest. He felt as if something were 'jumping' inside his chest. His pulse at the wrist was found to be only 20, while the venous pulsation in the neck, which was very marked, was 80 per minute. A soft systolic murmur could be heard now at each contraction of the ventricles. He was put on the X-ray screen, when thirty-two auricular contractions were counted to nine ventricular. The dissociation of rhythm was strikingly visible. He was given strychnine and caffeine, and soon a normal rhythm returned. Two days later the drugs were discontinued; within fourteen hours he had another attack. 'Everything in the room was turning round,' he said, and he was

evidently in great distress. The pulse at the wrist fell to 16, while the venous pulse was 90. He was given strychnine subcutaneously, and caffeine by the mouth. Again improvement rapidly followed. Under careful treatment the attacks diminished in frequency, though in one the radial pulse fell to 12. After about three weeks' freedom from attacks he had a series of very severe ones, being unconscious during the periods of bradycardia, and returning to consciousness as the pulse revived. He then passed into an epileptiform state, in which he bit his tongue and lost control over his sphincters, while his legs and back were quite rigid. For about three days he passed through these phases in turn: the ventricles stopped, he became unconscious; the pulse was revived, he became convulsed or excited. On several occasions competent observers believed him to be dead, yet on powerful stimulation the heart could be made to go on again, and he came back to life. At last it stopped for ever.

The heart was found to be only slightly hypertrophied, and there was a little atheroma of the coronary arteries. No other signs of disease could be made out anywhere until the muscular tissues in the neighbourhood of the auriculo-ventricular bundle were examined microscopically in serial sections, when degenerated fibres were found embedded in a mass of fibrous tissue.

2. Nodal Rhythm.—*Simultaneous auricular and ventricular contractions.* As an example of a less

profound departure from normal rhythm, which can also be explained by interference with the auriculo-ventricular bundle, we may take the irregularity seen in the later stages of mitral disease, especially mitral stenosis. James Mackenzie has called attention to the way in which the typical crescendo presystolic murmur may suddenly vanish. A diastolic murmur, diminuendo in character, may be present, but its method of production is different. The crescendo murmur is due to auricular contraction, while the diastolic murmur is due to the blood which has been stored up in the auricle during ventricular systole flowing through a constricted orifice as soon as the ventricle passes into diastole. The former is an active change, the latter is passive. At the same time the jugular pulse changes in character, presenting no evidence of an auricular contraction in the normal period. The question arises, What is the auricle doing? From the thinning and stretching of the auricular muscle often seen, it might be thought that it was paralyzed; but certain of the muscular fibres, such as the *tænia terminalis*, are hypertrophied. The auricular muscle must have contracted, but did not do so at the normal period. The auricle and ventricle appear to contract simultaneously. Now, the cardiac contraction starts at the part of the tube which is the most excitable; this is normally the venous end, but if another part becomes more excitable, the contraction starts from that part. Mackenzie suggests that in advanced mitral stenosis the distension of the

auricles interferes with the conduction of the stimulus, so that a break is made between the sinus node and the auriculo-ventricular node or *Knoten*. Contractions start now at the latter point. Lohmann found that when he experimentally stimulated the bundle at or near this node, the auricles and ventricles contracted simultaneously, which supports Mackenzie's interpretation. The disappearance, then, of the pre-systolic murmur denotes a further loss of compensation.

A similar disturbance of rhythm is met with in arteriosclerosis. In all such cases a marked degeneration of the coronary arteries has been found, when looked for, especially of that branch which supplies the *Knoten* and bundle. Mackenzie considers that at a stage in this degeneration the *Knoten* becomes more excitable than the sinus node, so that the contraction starts at that point.

These two types differ markedly in their reaction to digitalis. The results of a rheumatic endocarditis do not include degenerative changes in the auriculo-ventricular bundle as a rule, so that cases of mitral stenosis may respond well to digitalis. Once the tone of the stretched auricular fibres is sufficiently restored, this type of rhythm will disappear. But in the cases secondary to arterial degeneration, where an irritative degeneration of the *Knoten* is responsible, digitalis can have but little effect, and may have none. It is open to further objections, which will be discussed presently.

3. **Extra-Systoles.**—*Premature contractions of the auricle, or more usually of the ventricle, in response to a stimulus from some other portion of the heart than the sino-auricular node, but where otherwise the fundamental rhythm is maintained (Mackenzie).*

At first sight this condition seems the very opposite of heart-block. Instead of auricular contractions failing to reach the ventricles, ventricular contractions are initiated without waiting for a stimulus to pass down to them. On further examination, however, we shall find that, so far from being opposed conditions, they are often closely associated.

When Stannius tied his first ligature between the sinus and the auricles of a frog's heart, he found that he could generally arrest the auricles and ventricle. But when he tied a second ligature between the auricles and ventricle, the latter would assume a slow, independent rhythm. Gaskell explained this by the different character of the muscle at the two situations. The first ligature cut into a thin strand of muscle, dividing the fibres, and establishing a block, while the second, tied round much thicker muscle, bruised without dividing the fibres, and thus stimulated them. Thus we see that a slighter lesion of the auriculo-ventricular bundle might cause extra-systoles by stimulating it, while severe lesions might lead to complete heart-block. Mackenzie has observed this sequence of events in the same patient. And Keith has always found evidence of degeneration of the auriculo-ventricular bundle on examining the hearts

of patients who had showed extra-systoles during life.

The extra-systole is recognised by a premature beat in the radial pulse, followed by an abnormally long pause. On auscultation the regular sequence of heart sounds is occasionally interrupted by two sharp sounds (if very feeble, only one may be heard), followed by a long pause.

Patients who are suffering from extra-systoles may be conscious of abnormal sensations, such as a transient fluttering in the chest when an extra-systole occurs, or of the long pause, 'as if the heart had stopped,' or of the big thudding beat which frequently follows the long pause.

We have seen how an extra stimulus thrown into the heart muscle may fail to produce any effect if it falls within the refractory period, while if it is thrown in just after this, a small beat followed by a longer pause results. The analogy between the experimental and the clinical conditions is therefore very close. Mackenzie finds that it is the auriculo-ventricular bundle that is so refractory after the extra-systole, indicating that in its diseased condition a premature beat uses up so much of its energy that it is incapable of responding again for some time. He has even found that the wave may take a fifth of a minute to pass from auricle to ventricle, as measured by the interval between the auricular wave in the venous pulse and the carotid impulse. This interval rarely exceeds a fifth of a second in a normal heart.

It is important to recognise, however, that there are two groups of conditions under which extra-systoles are met with, and that their significance is widely different (Mackenzie):

1. Without organic change, as in the young and in those in whom extra-systoles appear at intervals and finally disappear.

2. In people of maturer years in whom it is found associated with sclerotic changes in the heart muscle.

Too much importance must not be attached to this type of irregularity *per se*. Mackenzie says: 'I have followed cases for many years, and watched them pass through seasons of sickness and of stress, and have seen no reason to attach any serious import to this symptom. What should weigh with us more is whether or no there is any contraction of the field of cardiac response. In early life the field is a constantly expanding one; in early middle age it begins to contract. But so accustomed does the individual become to its gradual variation that he readily notes the sudden decrease of the field. . . . When a patient presents himself for examination, and exhibits, it may be, a pulse with an occasional or even a frequent irregularity, or a pulse abnormally quick or abnormally slow, if there be entire absence of any cardiac enlargement and valvular disease, and the patient's field of response is what one would expect for his years, then we can safely assert that there is very little the matter, and for all practical purposes he is a healthy man. On the other hand, a man may

be seated in his chair feeling in good health ; . . . his heart exhibits no sign of any derangement, and his pulse seems good in every respect ; yet whenever this man walks a hundred yards he is suddenly seized with a spasm of angina pectoris. . . . The only symptom is a field of response so much contracted that we are obliged to take a very grave view.'

Some hearts are very sensitive to drugs, and will readily become irregular under the influence of tea, tobacco, or digitalis. Common sense will dictate abstention from them, if this be so. Irregularity of the pulse may be met with in cases of orthostatic albuminuria, where, as we have seen, the vasomotor tone may be defective. Here the heart is not necessarily 'weak,' as it is too often labelled, and the irregularity will subside when adolescence is past. It is our duty not to alarm a patient, already nervous, by the vague but terrifying diagnosis of weak heart. How many patients tell us that they are suffering from this condition in whom we are unable to find anything wrong whatever !

The following points in a case of extra-systole should lead us to form a more serious opinion :

1. If the irregularity does not disappear during an intercurrent febrile attack.

2. If the blood-pressure is persistently raised. This suggests arteriosclerosis, which may affect the vessels supplying the bundle, and thus in time lead to heart-block.

3. The appearance of even one small beat after the

big beat of an extra-systole. Mackenzie says that experience has told him that in people of mature years it is invariably associated with advanced degenerative changes in the heart muscle, and hence is a very valuable sign of myocardial degeneration. It is never seen after the extra-systoles of the young.

4. **Pulsus Alternans.**—*A regular succession of small and large beats.* Wenkebach explains this phenomenon as follows: When contractility is depressed, a strong and full contraction will encroach upon the period of rest, so that, by the time the next stimulus arrives, the contractility has not sufficiently recovered, and a smaller and shorter contraction results. As this contraction is shorter in duration, the period of rest is thereby lengthened before the next stimulus arrives, so that the next contraction will be longer and stronger, and so on. Now, one of the chief causes of a full and strong contraction will be increased resistance to the flow through the peripheral vessels, such as occurs in arteriosclerosis. And Mackenzie has found that high blood-pressure has an important influence in producing the pulsus alternans. In healthy hearts the period of rest is so long that a little increase or shortening has no perceptible effect upon the size of the beat, but in damaged hearts a very little variation in the period of rest has a manifest influence on the subsequent contraction. Whereas deficient conductivity will lead to heart-block and extra-systoles, impaired contractility will lead to the pulsus alternans. Of course, both functions may be

depressed, when extra-systoles may appear with the pulsus alternans, producing the most bewildering irregularities.

Summary.—Remains of the primitive cardiac tube are found in the mammalian heart at the sino-auricular node, the auriculo-ventricular node and auriculo-ventricular bundle. The sino-auricular node is only connected with the rest of this by ordinary cardiac muscle. These remains, like the whole heart of simpler vertebrates, have the power of originating a stimulus for contraction, of conveying the stimulus along the tube, and of contraction. In advanced mitral disease the stretching of the left auricle may interfere with the passage of the wave between the sinus node and the auriculo-ventricular node; in consequence the stimulus may originate in the latter instead of in the former, leading to the nodal rhythm, in which auricles and ventricles contract simultaneously instead of successively. Partial interference with the auriculo-ventricular bundle may lead to interference with the wave of conduction from auricles to ventricles, so that the part of the bundle below, which still retains its primitive power of initiating a contraction, starts an independent ventricular rhythm, the extra-systole. More complete interference with the bundle causes a more complete dissociation of rhythm, as is seen in heart-block. If it be the contractility rather than the conductivity of the bundle that is at fault, an increase in the work of the heart will lead to an alternation of large and small beats. Mere irregularity without any

limitation of the field of response need not be regarded seriously.

Treatment.—In the light of the new evidence we have got as to cardiac rhythm, the effects of the drugs in ordinary use for diseases of the heart will have to be reinvestigated. At present the data are insufficient, but a few conclusions have been arrived at.

Digitalis is by far the most potent of these drugs. but it is a two-edged sword, and very unsatisfactory results may follow its use in unsuitable cases. Besides its action on the heart, it has a pronounced effect upon the bloodvessels, causing vaso-constriction, and therefore a rise of blood-pressure. It is to be hoped that in time it will be generally realized that it is as rash to give digitalis without taking the blood-pressure as to give morphia without examining the urine. At present it is frequently prescribed for a heart that is failing behind a pressure that is already excessive. How can it be expected to be beneficial in such a case? In pulsus alternans also, where increased blood-pressure is an important factor, digitalis is inadvisable.

The blood-pressure should always be determined first, and if it be distinctly raised, strophanthus, which has a similar cardiac, but a much smaller vascular, effect, is preferable. Or if digitalis be used, a nitrite should be given also to act as a vaso-dilator. Cushny points out that as the action of digitalis sets in rather slowly and persists for a long time, while nitrites act rapidly, but are excreted comparatively soon, the best

results are obtained by frequent small doses of nitroglycerine, which need not be administered for some hours after the digitalis.

Turning from the vessels to the heart, we have to distinguish between the action of the drug on conductivity and on the force of contraction. On conductivity digitalis often has a depressing effect; Mackenzie has shown that it causes a delay, and sometimes a stoppage, in the transmission of the impulse from auricle to ventricle. Conduction is such an important function of the auriculo-ventricular bundle, that when this structure is involved, as in heart-block, digitalis is contraindicated. In many cases of heart-block the blood-pressure may be quite high, although the arterial pulse is so slow. Gibson has seen three cases in which the pressure ranged from 210 to 270 millimetres. In one such case, where the radial pulse was 32, while the venous pulse was 64, I found that the blood-pressure was more than 300 millimetres. Under these circumstances the reasons against digitalis are doubly strong.

On the other hand, when a nodal rhythm is found in mitral stenosis, digitalis is a most useful drug: Here the thinning of the auricular muscle interferes with the passage of the wave; the bundle itself is not at fault. This is remedied by increasing the tone of the auricles. The most striking and immediate benefit I have ever seen from digitalis was in a case of mitral stenosis with nodal rhythm and a blood-pressure of only 80 millimetres.

Caffein appears to be a good drug to use when the conductivity of the heart muscle is lowered, as it acts directly on the muscle fibres, increasing their irritability. The vagus also has less influence over the heart after caffein, and as one of the effects of vagal stimulation is to depress conductivity for the time, this drug is additionally serviceable. It is true that it will raise blood-pressure by acting on the vasomotor centre, so that similar precautions must be taken as with digitalis, though its influence is not so profound in this direction. Theobromine may be substituted with advantage if the pressure be raised, as its action on the heart is the same, while it has but little action on the vasomotor centre.

Of all drugs in the treatment of heart-block, strychnine has yielded me the most striking benefit; improvement has speedily followed so frequently that it cannot be a mere coincidence. Yet, according to Cushny, 'any improvement which may be produced by it (in heart disease) must be attributed to the constriction of the vessels, and the indications for its use would seem to be a low blood-pressure. . . . The heart rhythm is also slower after strychnine has been administered, owing to stimulation of the inhibitory centre.' I can only suppose that its tonic effect on a diseased bundle outweighs these drawbacks.

Thyroid extract has been advocated for heart-block by Gautier. Kidd observed some improvement during its use, but the patient was taking nitroglycerine and strychnine at the same time. Hay and

Moore gave thyroid extract an extended trial, but concluded that conductivity varied independently of the drug.

This is not the place to attempt to deal with the treatment of cardiac arrhythmia in general; my object is simply to call attention to certain modifications in our ideas which result from our fresh knowledge of the functions of the cardiac muscle.

Compensation.

Certain physiological principles will help to a comprehension both of the occurrence and of the failure of compensation.

If the cardiac muscle be exposed to an increase of its load, such as occurs when there is a greater resistance to the outflow of blood, it responds by increased energy of contraction. With each addition to its load there is additional shortening of the fibres. Of course, there is a limit to this, and, if the load be increased too much, the muscle may fail to respond at all. It has been said that the heart's motto is 'All or nothing': the tendency of the cardiac muscle is to rise to an emergency and do all that is required of it, but, if it be unable to meet the demands in full, to do nothing at all. In this we see the explanation both of compensation and of syncope; the muscle goes on responding until the proverbial last straw proves too much for it.

How great is this reserve force of the heart is seen by the experiment in which a ligature is placed round

the pulmonary artery and slowly tightened. The lumen of the artery may be reduced to one-third of its normal size without perceptibly diminishing the output of blood, though the intracardiac pressure will have to rise three- or four-fold. The same thing is observed if the work of the heart be augmented by increasing the diastolic inflow, either by pressure on the veins of the abdomen, or by injection of large quantities of fluid into the circulation, or by damaging the aortic valves. Within very wide limits, the output of the heart is independent of the resistance (Starling).

Complete failure of the whole heart to respond is exceptional; more usually the failure involves individual fibres. If the peripheral resistance be increased too much, the volume output of the ventricle will diminish, an increasing quantity of blood remaining in the ventricle after each systole. In this way dilatation will result. For continued additional work to be performed, hypertrophy of the cardiac muscle must occur. Its causation is obscure, but one result of the activity of the muscle must be an additional lymph flow, and increased nutrition would lead to increased growth of the cells.

When adequate hypertrophy has produced complete compensation, it may be asked, In what respect is the hypertrophied heart inferior to an ordinary one? It is powerful, and it can meet the demands made upon it, but it is definitely inferior in two points. It is working much nearer to the limits of

its power, so that it has much less reserve force, and its capacity for adjusting itself to unusual calls upon it is therefore restricted. It is, in fact, a spendthrift heart, while a dilated heart is a bankrupt one. Secondly, the auriculo-ventricular bundle does not hypertrophy with the rest of the heart, and a strand which may be adequate for the conduction of normal impulses may prove unequal to the continued carrying of the more powerful impulses which are now necessary.

Though the heart can adjust itself so well to increased resistance to its systolic output, it is very intolerant of interference with its diastolic filling. One important factor in this filling is the aspiration of blood into the chest by the respiratory movements. When persons are crushed to death in a crowd they die of syncope, not of asphyxia. Yet it is the compression of the thorax that kills, and children, with their comparatively yielding chests, suffer first. They die because the heart cannot be properly filled. Again, rupture of an aneurysm of the first part of the aorta into the pericardial sac may be immediately fatal, though only 6 or 8 ounces of blood are extravasated in some cases. No one dies from such a small loss of blood as that; death is not from hæmorrhage, but from the sudden rise of intrapericardial pressure, which prevents the diastolic filling of the heart. In pericardial effusion the accumulation of fluid is not so rapid, so that the heart has time to accommodate itself to some extent; but here, too, its action is

seriously embarrassed. A probable explanation of the contrast is that interference with the diastolic filling strikes at the very origin of the rhythm in the sino-auricular node, and deprives the heart walls of that tension which is so powerful a stimulus to contraction.

CHAPTER X

THE VASOMOTOR SYSTEM IN DISEASE

THE introduction of precise methods of registering blood-pressure in clinical work has naturally directed much more attention to the part played by the vasomotor system in disease.

Briefly, the functions of the vasomotor system are two—to regulate the general blood-pressure, and to regulate the local blood-supply. These functions are subserved by the following structures:

1. **The Vasomotor Centre**, beginning 1 or 2 millimetres below the corpora quadrigemina, and ending 4 millimetres above the calamus scriptorius. But there must also be secondary centres in the cord, since asphyxia can still produce a rise of blood-pressure after the medullary centre has been cut off, though not after the spinal cord has been destroyed. There is, further, some degree of local vasomotor control, since some recovery of tone may occur after complete separation of the vascular area from the central nervous system. This is largely dependent on peripheral ganglia, for whereas the bloodvessels of a

rabbit's ear soon regain their normal size after section of the cervical sympathetic, they remain permanently dilated after extirpation of the superior cervical ganglion.

2. **Efferent Nerves**, which can either constrict or dilate the vessels.

(a) *Constrictors*.—These are much the most numerous, and are confined to the sympathetic. Leaving the spinal cord in the anterior roots of the second thoracic to the second lumbar nerves, they pass into the sympathetic chain by the white rami communicantes, and end around a nerve cell in the first ganglion they reach. Here a new non-medullated 'postganglionic' fibre starts, which is distributed to its appropriate destination. This is the method of distribution, whatever the part of the body to be supplied.

(b) *Dilators*.—These are not nearly so numerous. The muscular coats of the bloodvessels being always partly contracted, it is possible for dilatation to be produced by inhibition of a constrictor. Pure dilator nerves will, therefore, only be found where there is a special need for marked and rapid dilatation. Thus the chorda tympani nerve carries dilator fibres to the submaxillary gland, and the auriculo-temporal nerve to the parotid. The nervi erigentes form part of the pelvic visceral nerve springing from the second and third sacral roots. All these belong to the *parasympathetic* system—*i.e.*, those fibres with visceral functions which leave the central nervous

system above the cervical or below the lumbar plexus. Unlike the constrictors, they have their ganglionic station close to their destination.

The existence of dilator fibres, also, in mixed nerve trunks has been proved by taking advantage of the fact that constrictors degenerate more quickly after section, and are more readily affected by cooling than dilators; on using slow, rhythmically repeated shocks (one per second) a dilator effect can be obtained, whereas rapidly interrupted shocks would excite the constrictors.

Dilator nerves to the limbs have appeared in a new aspect, however, since Bayliss has shown that they seem to be in every way identical with the sensory nerves. Under experimental conditions, at any rate, these fibres are able to carry 'antidromic' impulses—that is to say, the same fibre is able to convey sensory impulses towards the brain and dilator impulses towards the periphery. This is a disturbing fact, because opposed to our fundamental conceptions of the functions of the anterior and posterior roots, but it cannot be neglected on that account. The missing link in the evidence at present is the way in which these fibres are connected to the muscular coats of the vessels.

3. Afferent Nerves.—Impulses may pass to the vasomotor centre calling for a general rise or fall of blood-pressure. While the efferent nerves may produce either a local or a general effect, the afferent can only produce the latter. They are of two kinds :

(a) *Pressor*, producing a rise of blood-pressure. All sensory nerves are pressor in their action, causing the vasomotor centre to throw out increased constrictor impulses, particularly to the splanchnic area. This explains the rise of pressure which may be seen in all painful conditions. It has the effect of increasing the blood-supply to the brain; at the same time vaso-dilatation occurs at the site of the painful stimulus through the antidromic fibres. In this way the blood-supply is simultaneously increased at the point where the painful stimulus is *received* and where it is *perceived*, thus facilitating the appropriate reaction in each case.

(b) *Depressor*, producing a fall of blood-pressure by causing the vasomotor centre to relax the normal constrictor tone in the splanchnic area, which thereby becomes flushed with blood. The only pure depressor nerve is the depressor branch of the vagus. This may be regarded as a way of escape for the heart, if it be labouring against too high a blood-pressure.

The existence of depressor fibres in sensory nerves may also be demonstrated, since on regeneration after section they recover before the pressors, and on cooling they retain their function longer. Stimulation of the mucous membrane of the rectum and vagina may also produce a depressor effect, especially under anaesthesia.

Failure of the vasomotor system to respond adequately to the needs of the body may result either in insufficient regulation of the general blood-pressure

or of the local blood-supply. We will take examples of both.

It is not uncommon to be told by a patient that one of his first symptoms was that, on getting out of bed in the morning to pass water, he fainted. Normally a change of posture should not produce a perceptible effect on the blood-pressure, the slightest degree of cerebral anæmia at once inducing the vasomotor centre to throw out increased constrictor impulses, which, by tightening up the splanchnic bloodvessels, forces more blood to the head again. In this way the effect of gravity is counterbalanced. But if the vasomotor response is inadequate, the erect posture will lead to cerebral anæmia, and hence to fainting. If the intra-abdominal pressure is lowered at the same time by the emptying of the bladder, this is still more likely to happen. Fainting following the tapping of ascites is due to the same cause, and, as is well known, it may be prevented by tightening up a binder round the abdomen as the fluid escapes, thus avoiding the splanchnic engorgement that would otherwise occur.

During prolonged recumbency the vasomotor centre will lose its promptitude in responding to changes of posture, which explains the faintness that any patient is subject to on first getting out of bed after a long illness.

Insomnia may be due to inadequate control of the general blood-pressure by the vasomotor system. Ordinarily a certain degree of cerebral anæmia plays an important part in inducing sleep. The hypnotic

effect of taking some warm fluid or a little food is due to the vaso-dilatation it induces in the splanchnic area, thus drawing away blood from the head. Cold feet may play a part in causing insomnia by keeping too much blood at the opposite end of the body.

Insomnia, as we know, is often a troublesome symptom in conditions of high arterial tension. Apart from measures directed towards the cause of the high tension, we should treat this symptom by propping the head up on fairly high pillows, by flushing the abdominal vessels by a drink of hot water, and by preventing the feet from getting cold.

In 'functional' or orthostatic albuminuria, inadequate vasomotor control, as we have seen, plays an important part. The circulation through the kidney is therefore retarded by back pressure in the erect posture. Albumen, therefore, is present in the urine secreted in the day, but absent from that secreted while in bed.

Examples of failure in the regulation of the local blood-supply are seen in Raynaud's disease and in erythromelalgia.

At first sight it is not a little surprising that the organs concerned in the 'tripod of life'—the brain, the lungs, and the heart—either lack or are very scantily supplied by vasomotor nerves. Yet on consideration it will be clear that it is just because they are so important that they cannot submit to be subservient. For we must remember that the vasomotor system can override the local needs for the

general demands. The efferent path in a reflex arc is open to impulses coming from many quarters, although the afferent channel is reserved for impulses coming from the particular organ it supplies.

The organs composing the tripod of life cannot submit to having their local needs subordinated in this way. This may cause them in disease to override the interests of the general economy for their own advantage; though it is merely an example of the survival of the fittest, the most vital organs being protected at all costs.

It is for just such reasons that we find the spleen, a comparatively leisured organ, has its blood-supply most subordinated to the vasomotor system. It is the splanchnic area that plays the largest part in vasomotor effects. Now, it may well be that the stomach or intestines cannot spare their extra blood at a time when vaso-constriction is called for in the general interests of the economy. The spleen is a portal reservoir which will not suffer vitally from a vaso-constriction, and so it is called upon. It is because of its great liability to passive change and of its subordination to the general interests that diseases of the spleen are accompanied by so few definite physiological features. As Frederick Taylor tersely expresses it, the spleen is more sinned against than sinning.

The way in which the local needs may be overridden by the vasomotor system is seen in the blanched condition of the skin in the cold stage of fever, and in the dyspepsia that may be produced by

severe mental effort during active digestion through blood being forced into the head from the abdominal vessels, which are thus rendered too anæmic.

It will be convenient to consider some of the results of the exemption of the 'tripod' of brain, lungs, and heart from the operation of this action of the vaso-motor system.

Brain.—Munro, in 1783, enunciated the dictum that the quantity of blood in the cranium is a constant, since the brain substance is incompressible and enclosed in a rigid box. Allowing for variations in the quantity of cerebro-spinal fluid, this is true.

The first effect of a rise of arterial pressure will be to express the cerebro-spinal fluid from the cranium, and then to compress the cerebral sinuses until the pressure in them rises to that which the brain substance exerts against them. Thus the conditions approximate to those obtaining in a system of rigid tubes.

Now, the one part of the brain that must keep up its supply of arterial blood is the medulla, for here are the centres that are essential to life. If the blood supplied be too rich in carbon dioxide, the respiratory centre is excited to increase the respiratory rhythm; if the quantity of blood be not adequate, the vaso-motor centre is excited by the slightest degree of cerebral anæmia to contract the vessels in the great splanchnic pool, and thus force more blood up to the head. There are two ways in which the blood-supply to a part may be increased—local vaso-dilatation, or

vaso-constriction elsewhere. In a rigid box a local relaxation of muscular tone would not be very effective, for it might be overridden easily by the intracranial pressure already existing. To force the blood in by a general rise of blood-pressure is to employ a much more powerful mechanism. Thus it is we find that the blood-supply to the brain is mainly controlled by means of the splanchnic area, which, in its turn, is controlled by the vasomotor centre within the cranium.

This is not to say that there are no vasomotor nerves in the cerebral vessels—such have been found by Morison and by Gulland—and perfusion of adrenalin will cause some contraction of these vessels. But it is safe to assert that they must play an entirely subsidiary part, and that all the vasomotor effects ordinarily observed can be adequately explained without reference to them.

To avoid cerebral anæmia, the general blood-pressure must be kept at a point above the intracranial pressure. This was clearly proved by Cushing, who adopted the method of varying the intracranial pressure by introducing normal saline solution into the cranial cavity from a pressure-bottle.

The effect on the general blood-pressure was observed by means of a tracing taken from the femoral artery. Until the intracranial pressure exceeded the blood-pressure, nothing more than a slight quickening of pulse and respiration occurred, and even this could be avoided if the fluid did not

interfere with the sensitive dura. But when that point was reached, the blood-pressure was at once raised until it was again greater than the intracranial pressure. This was repeated with each increase of intracranial pressure until the blood-pressure was forced to a level considerably over 200 millimetres of mercury. Then the vasomotor centre began to show signs of giving way. The splanchnic vessels could be seen to contract every time the brain was compressed, and to dilate again as the pressure fell. If the pressure were raised too rapidly, the so-called major symptoms of compression might be produced—convulsions, evacuation of the bladder and rectum, cessation of the respiration and pronounced vagus effect upon the heart, often causing its complete arrest for from ten to twenty seconds. Then followed a release from this extreme vagus inhibition, and the vasomotor centre began to exert its striking influence. If the vagi were divided before the compression was applied, the blood-pressure could be seen to correspond even more closely than before to the degree of intracranial tension, always remaining slightly higher. If both vagi and spinal cord were thus divided, an increase in intracranial tension did not affect the level of the blood-pressure in the slightest degree, showing that the adjustment is brought about by constriction of the bloodvessels in the rest of the body.

The clinical importance of this in the treatment of cerebral hæmorrhage has been brought out by Leonard

Williams.* 'If we reduce blood-pressure—*e.g.*, by venesection or amyl nitrite—to the point at which the reduction will be effective in checking the hæmorrhage, we are obviously in danger of reducing it to the point at which the medulla is starved. There may be a margin of safety—a point to which you may reduce the blood-pressure so as to moderate the hæmorrhage—without seriously diminishing the supplies to the medulla; but surely this is a razor's edge on which no practical physician will voluntarily choose to tread. The manometer has no information to give us on this crucial point. It tells us, no doubt, that the arterial pressure is very high, but we know that the arterial pressure was high before the accident, and that it is now higher still, because it has to overcome an augmented intracranial pressure; but the instrument does not, and cannot, tell us whether we ought to bleed the patient at all, and, if so, what are the danger-signals. For there are no danger-signals. When the arterial pressure is reduced below the intracranial, death is instantaneous. That venesection may be resorted to in apoplexy not only with impunity, but with conspicuous benefit, is a fact which must be accepted on the testimony of very competent physicians; that it is at best a dangerous expedient, dangerous to the life of the patient and extremely dangerous to the reputation of the practitioner, the above considerations are surely sufficient to show.'

* *The Hospital*, December 14, 1907.

The absolute necessity of maintaining the blood-pressure at a higher level than the intracranial establishes a vicious circle, for the hæmorrhage produces a rise of pressure, and the rise of pressure increases the hæmorrhage. A rising blood-pressure in cerebral hæmorrhage is of very grave prognosis, as it shows the bleeding is still continuing.

Cushing's experiments also explain why we so frequently find more than one hæmorrhage into the brain substance, if the initial one be at all large. If looked for, small hæmorrhages into the pons will be found very commonly in cases of ordinary lenticulo-striate hæmorrhage. It was formerly a puzzle to decide how these were produced, and whether they occurred simultaneously with, before, or after the large hæmorrhage. It is now clear that the large hæmorrhage is responsible for driving up the general blood-pressure so much that diseased arteries in other parts of the brain are unable to withstand the strain.

Lungs.—The absence of direct vasomotor effects in the pulmonary vessels has some interesting bearings on the treatment of hæmoptysis, which have already been touched upon in the first chapter. It must be remembered, however, that the lung receives blood by another channel also, the bronchial arteries, springing from the aorta. In the hæmoptysis of mitral stenosis the pulmonary vessels alone are involved; adrenalin and other constrictors will therefore do harm by forcing blood from the systemic into the pulmonary vessels. But amyl nitrite will do good,

because it will relieve the engorged lung by dilating the systemic vessels. In the hæmoptysis of phthisis, either pulmonary or bronchial vessels may be eroded, though the former are more likely to be implicated, since they are more numerous. But styptic drugs would be inadvisable even if we could be sure that a bronchial artery were the source of the hæmorrhage, for any benefit derived from their local action would be outweighed by the general rise of pressure and by the pulmonary turgescence, which might cause other weak spots to rupture. Nitrite of amyl would still be useful, as the widespread dilatation would draw blood away from the lungs, and thus more than counterbalance the risks of reopening the bleeding-point. Also the lowered pressure would favour the sealing of this point by blood-clot. The same principles would therefore guide us, whichever set of vessels were involved.

Leonard Williams (*Clinical Journal*, October 2, 1907) thinks that, as the blood-pressure is already low in phthisis, a vaso-dilator may be dangerous, since it might diminish the supply of blood to the medulla to a level incompatible with life. The consensus of opinion seems to be in favour of taking a little risk to secure the undoubted advantages of the treatment.

Œdema of the Lungs is a common terminal event. In Cohnheim's phrase, a man does not die because he gets œdema of the lung: he gets œdema of the lung because he is dying. It is held to indicate a some-

what rapid failure of the left ventricle, while the right ventricle continues to beat forcibly. As there is no vaso-constrictor action in the pulmonary vessels, there is nothing to prevent engorgement of the lung capillaries, and an effusion must occur into the alveoli. Recently Leonard Williams* has called attention to an acute form of this œdema, and from the correspondence which followed his communication it is clear that the condition is not uncommon, though very inadequately recognised in this country.

A patient usually with high blood-pressure and often with aortic disease is seized, generally while recumbent, with sudden dyspnoea and cyanosis. He becomes greatly distressed, throwing himself about or coughing incessantly. Then a quantity of froth, which has been compared to that of beer, only finer and thinner, and often blood-stained, begins to issue continuously from nose and mouth. Death may occur within a few minutes, and will not be delayed beyond a few hours, if the condition cannot be relieved.

As the heart continues to beat strongly after the patient is apparently suffocated, it might be urged that death could not be from syncope. But it is probable that the forcible sounds are produced by the right heart. The most probable sequence of events is this: The left heart is already loaded to its full capacity; the proverbial last straw is too much for it, and it breaks down, while the right heart goes on

* *Lancet*, December 7, 1907.

beating still, forcing blood into the lungs until they become engorged, since they are quite unable to shut off any of the blood-supply by vaso-constriction. An outpouring of serum occurs into the alveoli in such quantities that the patient is drowned in his own secretion. Two facts support this view: the commonest cardiac lesion in these cases is aortic regurgitation, which is known to terminate not infrequently in sudden stoppage of the heart; and venesection (10 to 12 ounces), according to French authorities, is the only effective treatment, and this would relieve the overloaded right heart and the stagnant pulmonary circulation.

In *Spasmodic Asthma* the use of vaso-dilator drugs deserves consideration. The two principal views of asthma are: (a) That it is due to spasm of the bronchial muscles; (b) that it is caused by a vasomotor turgescence of the bronchial mucosa, producing similar changes to those seen in the nose in hay fever. The fact that antispasmodics do good might be taken as evidence in favour of the first view, and it might be argued, as against the second view, that if there are no vasomotor nerves in the lungs, an antispasmodic could have no influence; while if there are such nerves, the drug could only increase the turgescence. But this would be to neglect the fact that the vascular condition of the lung is so largely passive, and dependent on the systemic circulation. Hare believes that there is a vasomotor spasm in the systemic circulation, which

would cause a secondary and passive engorgement of the lungs. This would certainly explain the value of amyl nitrite in the asthmatic paroxysm, and of iodide of potassium in warding off attacks. But when he goes on to urge in support of this view Hyde Salter's observation on the smallness of the pulse during the paroxysm, we are compelled to remind him that constriction of the arterioles could not diminish the pulse-wave ; while the fixation of the chest, which occurs in the attack, must interfere with the diastolic filling of the heart, and thus lead to a small pulse through diminished output during systole.

Heart.—It is not difficult to understand the absence of vaso-constrictors to the coronary arteries. If a rise of general blood-pressure is produced by vaso-constriction, the heart is given more work to do, so that a better blood-supply must be given to its muscle. If vaso-constriction took place in the coronaries, the blood-supply would be diminished, but in its absence the rise of pressure automatically forces more blood into them. If the heart has less work to do, the pressure falls and the coronaries receive less blood. In this way the supply to the heart muscle is made proportional to its requirements. The power of compensation is extraordinary so long as the coronary arteries remain supple, but if they become atheromatous, this means of regulation is frustrated, and compensation breaks down.

The heart's ties with the vasomotor system are most intimate on the afferent side through the

'private path' of the depressor nerve. Through this the heart can always produce a fall of pressure should it find itself embarrassed by a pressure that is too high for it. It might be thought that under these circumstances an abnormally high pressure could never be maintained. But so long as the heart can meet the high pressure, there is no inducement for it to call the depressor nerve to its aid. We may safely assume, however, that when the pressure is kept up at a point at which the heart begins to dilate, a structural change must have occurred in the walls of the visceral vessels which renders them incapable of relaxing in answer to the appeals of the depressor nerve.

On Blood-pressure.—The vasomotor system is, of course, only one factor in determining the blood-pressure. Its importance lies in its sensitiveness to the needs of the organism; like all nervous mechanisms, it is characterized by the rapidity of its reactions.

The pressure, by which the whole of the vascular system is kept distended with blood, is the product of—

1. The beat of the heart.
2. The peripheral resistance.
3. The elasticity of the vessel wall.
4. The volume of the blood.

1. While the energy of the heart necessarily originates the pressure in the vessels, an increase in its output will cause a rise in pressure only so long as

the size of the arterioles remains the same. Mere increase in frequency also will not raise pressure, unless there is a large amount of blood in the great veins awaiting entrance into the heart, and the peripheral resistance is adequate. Indeed, the nervous mechanisms provide that the pulse-rate will vary almost inversely with the blood-pressure. If the pressure rises to a point at which the cardio-inhibitory centre in the medulla is stimulated, the heart is slowed through the vagus, so that unnecessary work is avoided.

2. The effective peripheral resistance is provided mainly by the constriction of the muscular coats of the small arteries, which are chiefly controlled by the vasomotor nerves. That the capillaries can change their calibre under the influence of chemical stimuli is, however, highly probable, and the arterioles themselves are not unresponsive to such. Thus Gaskell showed that the acid products of metabolism would dilate the peripheral vessels, and thus provide for their own removal. It is now generally agreed that in the first stage of high blood-pressure in disease there need be no structural change in the vessel wall, but that the muscular coat contracts presumably under the influence of toxic agents. This is in accordance with the general principle that the important functions are subserved by both a chemical and a nervous mechanism. How essential the nervous factor is in maintaining the pressure is seen on destruction of the cord, when the vessels lose their

tone so completely that the circulation cannot proceed. It is the splanchnic area which has in this way by far the greatest influence on the general blood-pressure.

3. The elasticity of the vessel wall tends to equalization of the pressure in systole and diastole. For, as the vessel distends with each heart-beat, the pressure becomes lower, and as it retracts during diastole, the pressure remains higher than it otherwise would do. With loss of elasticity comes a more violent fluctuation. According to Roy, the elasticity of the vessel wall is greatest at about the normal pressure. With an increase in pressure, then, the distensibility of the arteries diminishes, and an increased output now raises the pressure at each beat more than it would normally. Mark the tendency to a vicious circle. Continued high pressure diminishes elasticity, thus increasing the work of the heart. The heart has to hypertrophy, and each beat produces a still higher systolic pressure in a tube that is becoming more rigid. The sequel must be that either the vessel gives way, forming an aneurysm, or rupturing, or else the heart dilates behind the strain.

From this point of view the formation of an aneurysm is a conservative measure, though one of a desperate character, to compensate for the raised pressure in an inelastic tube. This is supported by the observations of O. K. Williamson (*Lancet*, 1907, vol. ii., p. 1516), who found that the arterial blood-pressure in most cases of aneurysm of the

thoracic aorta or the innominate artery is either normal or slightly above normal. The average systolic pressure in his cases, with an average age of forty-seven years, was 134 millimetres, while in dilated aorta without aneurysm he found an average pressure of 185 millimetres. High pressure is, of course, sometimes present in aneurysm, when, according to Janeway, it is one more element in the already unfavourable prognosis.

4. The volume of the circulating blood has within wide limits in the normal animal only a subordinate and temporary influence on mean blood-pressure (Janeway). Its variations can be easily compensated for by the vasomotor system. This limits the usefulness of venesection to those cases where the compensating mechanism has become damaged. Thus, if the right auricle is becoming so dilated that the transmission of the wave of contraction to the ventricle is a matter of difficulty, venesection may permit it to regain its tone; or if the responsiveness of the vasomotor system is becoming dulled by arteriosclerosis or toxic agents, reduction of the volume of the blood by bleeding can diminish tension.

The blood-pressure in a normal individual reflects the influence of the various physical and mental states; a cold bath, a meal, the smoking of a cigar, an animated discussion, all show an effect upon it. There are also small diurnal variations irrespective of such disturbances. It might be questioned whether this does not do away with the value of a blood-

pressure record. But no one questions the value of a temperature chart which also shows fluctuations not produced by disease. And no one doubts the importance of a pulse record, although nervousness affects the pulse far more than it does the pressure. The alterations of pressure in disease far exceed these minor changes. It is of course necessary to make the observations under similar conditions and at the same time of day.

The clinical value of observations on the blood-pressure is only doubted by those who have never used them. Unlike many another apparatus, there is no sign of the sphygmometer being abandoned by those who have once employed it systematically; they only change the form of apparatus as mechanical improvements are made. The finger can detect some differences in pulse-tension, it is true, though it is often entirely at fault, since it can only estimate total pressure; so can the hand detect differences in temperature. But what opinion should we form of a physician who told us that he only judged of temperature by the hand and scorned the aid of the thermometer?

The only satisfactory methods in use depend on the same general principle—circular compression of the upper arm by an air-pad, adjusted by an armlet not less than 12 centimetres wide, to which a manometer is attached. Air is pumped in until the pulse is obliterated at the wrist, and then cautiously allowed to escape again until the pulse just returns. Janeway

regards the moment of return of the pulse-wave as the best criterion of systolic pressure ; some observers take the mean between this and the point of obliteration. It is doubtful whether any of the apparatus in use accurately record diastolic pressure, but so far the systolic pressure has proved of more interest in practice.

I employ Oliver's apparatus (made by Hawksley), where the manometer is a closed tube with coloured alcohol for the index, because it is so much more portable than any of those in which mercury is used. It is also much easier to read, since the oscillations of the fluid are much smaller than with the open mercurial tube. These advantages are specially pronounced in the latest form of Oliver's apparatus, where compression is applied quite steadily.

I shall use the term 'blood-pressure' as identical with the pressure recorded by some such apparatus. Opinions differ, however, as to whether this does not represent in reality the sum of the pressure and the resistance offered by the arterial wall. Gumprecht gives physical reasons for believing that the elasticity of the tube itself does not come into the question, and Janeway concludes that, with the wide armlet, and using the first full return of the pulse as a guide, errors from thickening or calcification of the wall have little significance. William Russell strongly dissents from this view, and it really does seem almost incredible that the great structural differences which are found in the wall can have no effect. But even admitting that the record is a composite one of

the resistance of the wall plus the pressure of its contents, this does not deprive it of its value, and changes of pressure as a result of treatment would still be accurately recorded.

If the manometer had done nothing else than teach us when not to give digitalis, it would have justified its existence. This has already been dealt with on pp. 165 and 262.

It is impossible to discuss the whole question of blood-pressure in disease within the limits at our disposal, but we may take examples of the way in which its study has enlarged our ideas, cleared up difficulties in diagnosis, and helped in prognosis. This has naturally reacted on treatment.

It has enlarged our ideas on the subject of the 'heart failure' in acute infections (see p. 21) and in post-operative shock. Romberg and Pässler showed that, at the height of an infection, sensory irritation and asphyxia did not produce as large a rise of pressure as usual, while abdominal massage raised it as much as ever. It is the vessels that are paralyzed, not the heart that is damaged. Recognition of these facts should lead us to realize the necessity of attacking the circulation through the vasomotor system when this is at fault, and thus protect the heart from secondary damage and needless or harmful stimulation. The surgical aspects of the question, which were so ably investigated by Crile and by Lockhart Mummery, have been lately reviewed in an interesting paper by Walton (*Lancet*, 1908, ii., pp. 17 and 85).

In the light of the knowledge we have thus obtained, it would appear that many of the stimulants employed are quite unsuitable for a condition which is really one of vasomotor paralysis. Strychnine acts on the centres, which are already exhausted or intoxicated, and therefore unresponsive. Ether has little or no effect; while brandy, which is a vaso-dilator, can hardly benefit vessels that are already relaxed. Digitalis, which acts on the peripheral vessels as well as on the heart, may be of service. Adrenalin and ergot, which act peripherally, may have an admirable effect in combating this paralysis; while barium salts—*e.g.*, 3 grains of the chloride—which act directly on the muscle fibre, and not even on nerve-endings, are appropriate. An abdominal binder should be applied firmly to prevent accumulation of blood in the now stagnant splanchnic pool.

As examples of the help which has been given in diagnosis, if we are in doubt whether a hemiplegia is due to hæmorrhage or thrombosis, we may appeal to the manometer; in the former the pressure must be high, from reasons already considered, while in the latter it need not. Grainger Stewart has shown that the fatal issue in cerebral thrombosis is often due to a rise of pressure in the stage of reaction, or as a result of stimulant treatment, which bursts the now softened vessel. In the treatment of cerebral thrombosis, then, we must be very careful not to use any stimulant which will raise blood-pressure.

The fact that perforation in typhoid fever causes a

rise of pressure, while hæmorrhage produces a fall, is one that will often be of great value in diagnosis.

In albuminuria, again, the blood-pressure will be an aid to diagnosis. In all forms of nephritis it is usually raised. Mahomed found that in acute nephritis the arterial tension rose even before albumen appeared in the urine. But in 'functional' orthostatic albuminuria, though the pressure fluctuates, it does not rise above normal. As the treatment demanded in the two conditions is diametrically opposite, it is essential to be clear which we are dealing with; and the manometer will help us. I have stated (p. 182) the grounds for my belief that it will help us also to decide on the relative importance of albuminuria and glycosuria when they coexist.

As to prognosis, the grave import of a continued rise in pressure in cerebral hæmorrhage has already been insisted on. In pneumonia a continued but gradual fall of pressure is the rule. Gibson finds that any sudden rise before the crisis implies the onset of some complication, acute delirium being often the immediate sequel, while a sudden fall is a warning of the immediate risk of cardiac (or, as I should prefer to express it, vasomotor) paralysis. In Addison's disease a steady fall of pressure, despite adrenalin, has enabled me to foretell the imminence of the fatal issue.

It is now generally conceded that there is a stage in which the blood-pressure is raised before the structural changes of arteriosclerosis occur, and

the manometer will help us to detect it. To take an example: A busy man nearing fifty years of age, and leading the active life of his time, on walking rather smartly to catch his morning train, finds himself out of breath for some little time afterwards. On arrival at his office he has a difficulty in concentrating his mind on his work, and on rising quickly from his chair at the end of the morning he feels very giddy, and reels a little. Now, a little anxious about himself, he becomes introspective—a rare thing with him—and recalls that small worries have upset him more than they need, that responsibility has been more irksome, and that he has not felt so sure of his judgment. He tells his partner that he thinks he has been out of sorts lately, and is met with the frank reply that it is very likely, for, at any rate, his temper has been shocking. He goes to lunch, and thinks that a whisky-and-soda will put him straight. But it doesn't; it only makes him feel more uncomfortable. He lights a good cigar, and is rewarded by palpitations, instead of the blissful sensations that smoking used to evoke. He remembers now that alcohol and tobacco do not seem to have agreed with him as they used. By the end of the day his head is aching, and he feels thoroughly worn out. He manages to eat a very good dinner as usual, however, and begins to shake off some of his fears. But his night's rest is disturbed, and next morning he feels very 'bilious,' or perhaps he has a return of the neuralgia that has been troubling him

of late. It will be a good thing for him now if a violent attack of epistaxis occurs, if only to send him to his doctor. The doctor takes a heavy responsibility upon himself if he simply reassures him, tells him he is run down, prescribes some strychnine, advises a good piece of steak for lunch, and some fine old port after dinner. A more careful examination would certainly have revealed an accentuated second sound at the aortic base, and a blood-pressure of 160 to 180 millimetres; possibly also a trace of albumen, with granular casts in the urine. Even if the pressure is not estimated, the stability of the pulse may give valuable information. Normally, the pulse-rate is 8 to 10 per minute faster in the erect than in the recumbent posture; if this is not the case, we may infer that the blood-pressure is too high, so that the cardio-inhibitory centre in the medulla is stimulated more than it should be: hence the absence of quickening.

The responsibility is all the greater because this man is still in the stage when treatment can be effective; and he is more likely to abide by it than the lower type of patient, 'full of coarse strength, butcher's meat, and sound sleep, who will suspect any philosophical insinuation, or any hint for the conduct of his life which reflects upon this animal existence.'

Perhaps it is even better for him if the danger-signal takes the form of an attack of hæmaturia, for he is not likely to try home remedies for this, as he

may for epistaxis; nor is there much fear of the doctor treating it so lightly.

This may be simply the stage of increased blood-pressure, without structural change, produced by toxic agents. If in this stage the patient takes less meat and no alcohol, gets more oxygen into his lungs and a better evacuation from his bowels, leads a simpler and less strenuous life, an improvement in his blood-pressure and his general condition will follow. Potassium iodide should be given with a view, as Leonard Williams says, 'of ferreting out such of the toxins as seem to lurk in the lymph spaces.' There is too great a tendency to employ drugs that simply lower pressure by vaso-dilatation, such as nitro-glycerine or erythrol tetranitrate. This is, perhaps, not to be wondered at. In the early days of antipyretic drugs there was a similar tendency to indiscriminate lowering of the temperature. It is so pleasant to see some objective result from our treatment, and the manometer provides us with such a striking demonstration of the effect of these drugs. But the rise of pressure is a symptom just as surely as a rise of temperature, and to lower either without due consideration is to side with the toxin rather than with the patient.

If this high pressure continues, a structural change will follow. Dixon has shown that any drug which has the power of considerably raising blood-pressure will bring about degeneration of the middle coat of the arteries in a healthy animal. This might happen because the same drugs which raised pressure were

toxic to the arteries, or because the rise of pressure mechanically damages the wall. That the latter explanation is the correct one has been shown by Harvey, who, by merely compressing the aorta of rabbits with the fingers for two or three minutes daily, thereby raising the blood-pressure 30 to 40 millimetres, produced degeneration of the aorta above the point of compression without causing any change in the vessel below.

Tobacco is known to raise blood-pressure, and it might be thought to play a part in the much greater frequency of arteriosclerosis in men than in women. But tolerance is very easily acquired. If a man unused to tobacco smokes a cigar, his pressure first rises 10 to 25 millimetres, and then, after a quarter or half an hour, if the smoking has been continued, drops 30 or 50 millimetres, or even more. The habitual and moderate smoker under similar conditions shows no change beyond a slight rise of 4 or 5 millimetres. According to Emerson Lee, this immunity is brought about by the production in the liver of some substance—probably a ferment—that destroys the nicotine. We therefore cannot throw much of the responsibility for arteriosclerosis on to tobacco.

It must be admitted that we have a very hazy notion as to the nature of the toxic substances concerned, but the course of events may be pictured somewhat as follows: The toxin, whether formed by perverted metabolism or absorbed from the bowel,

irritates the muscular coats of the smaller vessels to contraction, particularly in the splanchnic area, where it will be present in the highest degree of concentration. Finally, it is excreted by the kidney. If this condition be allowed to continue, and the irritated vessels maintain their contraction, muscular hypertrophy must occur here as elsewhere when increased work has to be done. The new muscular tissue soon undergoes degenerative changes. The increased peripheral resistance thus brought about necessitates, for similar reasons, hypertrophy of the heart. The kidney has to excrete the toxin, and suffers in the attempt, so that interstitial nephritis is apt to follow. The pressure has now to rise still more, causing more cardiac hypertrophy in order to drive enough blood through the remaining glomeruli for urinary excretion. Even so elimination becomes defective, and the toxin is therefore kept in more prolonged contact with the tissues it is damaging. Thus, the diffuse arterial change steadily progresses. On this view the cardiac hypertrophy is purely secondary. Allbutt protests 'against the accusation of these striving hearts of complicity in the arterial disease. . . . They are stout and faithful to the end, even in defeat.'

This, of course, does not exhaust the forms of arteriosclerosis, but only deals with that in which the vasomotor mechanism is essentially involved. Allbutt's convenient classification of these types may be adopted. Excluding all cases of chronic Bright's

disease, he holds that arteriosclerosis is met with clinically in three forms—forms, if superficially alike, yet very different in nature and causation :

(a) *Toxic*, due to lead ; to certain of the infective diseases, such as syphilis ; to diabetes, and so forth.

(b) *Involutionary*, a senile degradation, which may appear before ‘ three-score years and ten.’

(c) *Secondary* or *hyperpietic*, the consequence of tensile stress, of excessive arterial blood-pressure persisting for some years.

The type previously described corresponds to (c) on this scheme. In the others there is not necessarily a rise of pressure, and we can probably refer the apparent rise, as registered by the manometer, to increased thickness of the walls. The so-called ‘ *rise of blood-pressure in later life*,’ occurring in healthy individuals, is probably due to this, and is merely an expression of that loss of elasticity which is characteristic of advancing years. The distinction between the cases in which there is a real rise of pressure and those in which there is not is a practical one. For, to quote Allbutt again, ‘ in involutionary arteriosclerosis, as time goes on, the vessels attain greater degrees of contortion than in the hyperpietic cases, and, grotesque as may be their deformity, result rather in the contraction of the spheres of mental and bodily activity than, as with hyperpiesis, in the imminence of the fell sergeant Death—death by apoplexy, by cardiac defeat, or by intercurrent acute pneumonia.’

CHAPTER XI

ON CYANOSIS

THE essential cause of cyanosis is deficiency of oxygen in the red corpuscle, while the essential cause of dyspnœa is excess of carbon dioxide in the respiratory centre. It will follow that, although these two conditions are often associated, this is not necessarily the case. Thus in uræmia we may see dyspnœa without cyanosis, whereas in congenital heart disease cyanosis occurs without dyspnœa.

A chemical change, then, which results in the hæmoglobin combining with less oxygen, is the immediate cause of cyanosis. But we must remember that in coal-gas poisoning the corpuscle contains less oxygen, and yet there is no cyanosis. The new compound carboxyhæmoglobin is a bright cherry-red. Again, in methæmoglobinæmia the corpuscle contains as much oxygen as normal, and yet there is marked cyanosis. We can distinguish two groups of cases, toxic cyanosis and true cyanosis. As we shall see, true cyanosis—*i.e.*, one due to simple reduction of the oxyhæmoglobin—is usually associated with an

increase in the number of the red corpuscles. In all cases of cyanosis in which the corpuscles are decreased, or even not increased, a toxic cause should be suspected.

Toxic Cyanosis.—In Chapter VIII., when intestinal intoxications were considered, it was shown that certain coal-tar drugs or nitrite-producing microbes in the intestine may cause methæmo-globinæmia, which may produce a striking degree of cyanosis. The condition can readily be detected by the spectroscope. Under conditions of intestinal intoxication associated with constipation, sulphæmo-globinæmia may occur also, which requires to be distinguished from the other toxic change in the hæmoglobin molecule. It is unnecessary to repeat what has already been said on that point, beyond urging the necessity of diagnosing this condition from the rest.

True Cyanosis.—It is important to observe that Nature's method of compensation for defective oxygenation of existing corpuscles is by adding to their number. Thus we find that prolonged residence at high altitudes, such as Quito in Mexico, results in a polycythæmia. The diminished oxygen tension at that height necessitates an increase in the number of oxygen carriers, so that, though each is capable of carrying less, the total amount of oxygen carried to the tissues remains the same. Applying this fact to diseases associated with polycythæmia, we should expect to find that the element of defective oxygenation enters into their etiology.

Erythæmia (Splénomegalic Polycythæmia).—The most striking example of increase in the red corpuscles occurs in the condition first described by Vaquez in 1892. Our knowledge of this disease has been added to by the observations of Osler, Saundby and Russell, and Parkes Weber. The patient is usually in the middle period of life. He is generally, though not invariably, cyanosed, but there is no respiratory distress. The eyes may be prominent and the conjunctivæ suffused. Examination of the blood shows that the red corpuscles are increased from the normal 5,000,000 to a figure varying between 8,500,000 and 12,000,000 per cubic millimetre, while the hæmoglobin is raised to 120 or 150 per cent. The white corpuscles are usually increased from the normal 8,000 to 20,000 per cubic millimetre, but in some cases are actually diminished. The viscosity of the blood is naturally considerably increased. The spleen is usually enlarged; sometimes it is greatly enlarged, but then infarcts or tubercles have been found in some of these cases. The urine frequently contains a trace of albumen. Pigmentation of the skin has been noted. The most prominent symptoms are torpor, both mental and physical; a sensation of fulness in the head, with headache and vertigo, and in some cases nausea and vomiting. As Osler has pointed out, these symptoms remind us of those to which mountain-climbers and aeronauts are liable. Certain vasomotor symptoms also call for attention. If any part be rubbed it goes red, and if the patient gets

hot the general cyanosis is apt to be replaced by a general flushing. A dependent part becomes blue, but if it be held up it may become pale. The vessels must be very full, for the volume of the blood is increased. Now the capacity of the vessels may be increased by relaxation of the vasomotor tone, and this loss of tone causes the effect of gravity on the circulation to become more pronounced. By the relaxed state of the vessels we can also explain the fact that the blood-pressure is not necessarily raised, although the vessels are so turgid.

The increased viscosity of the blood is a necessary result of its concentration from excess of red corpuscles. Gustav Mann has calculated that the maximum number of corpuscles which the blood is capable of holding in each cubic millimetre is 13·9 millions. A blood-count of 12,000,000 must imply, then, a very great increase in the viscosity of the blood, and therefore a considerable delay in the circulation time through the capillaries. This, in fact, has been experimentally demonstrated. Anything which increases the stay of the blood in the capillaries allows of the abstraction of more oxygen from it. We should therefore expect that this cause of cyanosis must be diminished in part by stimulating the rate of the circulation by warmth and friction, as is actually the case.

The polycythæmia remains to be explained. That it is a compensatory mechanism is shown by the increase in the erythroblastic tissues in the red

marrow. The enlargement of the spleen is perhaps to be explained in the same way; it may resume its foetal blood-forming functions. The other alternative is that its enlargement is purely passive from the relaxed state of the muscular coats of its vessels. Increase of the red marrow may be due to excessive destruction of blood-corpuscles, as in pernicious anæmia. The frequent presence of nucleated red cells shows how severe the strain on the blood-forming organs must be. But in erythæmia there is no evidence of hæmolysis, and the excess of red cells must be compensatory for difficulty in oxygenation somewhere. There are three possible ways in which this might occur :

1. A defect in the taking up of oxygen in the lungs.
2. The presence of a reducing agent in the blood.
3. A difficulty in the taking up of oxygen from the blood by the tissues.

The first is the cause of cyanosis in pulmonary diseases, but cannot be the cause here, since in that case a mere increase in the speed of the circulation would increase the cyanosis, as it would diminish the time given for oxygenation in the lungs.

As to the second possibility, Boycott has tested the oxygen capacity of the hæmoglobin, and found that, though in one instance it was slightly lessened, in another it was normal. And even in the first case the excess of hæmoglobin led to the total oxygen capacity of the blood being at least 10 per cent. more than

normal. And one case in which the oxygen capacity per cent. was normal is sufficient to dispose of the possibility of an abnormal reducing agent in the blood.

We are forced to accept the third explanation: there must be some difficulty in the taking up of oxygen by the tissues. Now, the materials out of which the tissues are made are comparatively stable, not being oxidized readily; yet we know that the tissues have an extraordinary avidity for oxygen. How are we to explain this apparent paradox? From normal tissue cell substances, presumably ferments, can be extracted, which are capable of effecting oxidations; to these the name of oxydases has been given. It seems necessary to postulate a diminution in the oxydases of the tissue cells; this granted, all the rest follows inevitably—deficiency of oxydases would cause the oxygenation of the tissues to be defective, which would increase the demand for red corpuscles. Hence the polycythæmia and the increase in the red marrow and the spleen. The excess of corpuscles would increase the viscosity of the blood, and this in its turn would cause a delay in the circulation time. Cyanosis occurs only when the delay is sufficient to allow of the tissues being able to take up enough oxygen, even though they can only do it slowly. The cyanosis disappears when the circulation is quickened in any way, and in some cases, such as the one so carefully described by Parkes Weber, it is never present. It may be urged

against this view that, as the polycythæmia is a compensatory mechanism, it would never occur up to the point of causing cyanosis, since this means an increased and not a diminished reduction. But it must be remembered that a compensatory mechanism is never so perfect as a normal one; if it were, it would tend to replace the existing one on ordinary evolutionary principles. The drawback to polycythæmia as a compensatory mechanism is the excessive viscosity of the blood which must accompany it, so that it becomes a difficult matter to provide the oxygen required by the tissues without delaying the circulation too much. If this happy mean cannot be exactly achieved, cyanosis must be caused, but this is less serious than starving the tissues of oxygen.

Treatment.—Until we can find some way to control the intracellular oxidation, there can be no effective treatment for this disease. That oxygen inhalations are no good is only what we should expect, as there is no deficiency of oxygen in the blood. Temporary benefit may be derived from bleeding. X rays have been applied to the spleen also, but without much avail, as we might expect, since the seat of the disease must be in the tissues.

Cyanosis in Congenital Heart Disease.—The cause of cyanosis in congenital heart disease has provoked so much discussion that it may be rash on my part to assert that the explanation is fairly simple, if we bear in mind the changes which ought to occur in the circulation at birth.

During foetal life the circulation is so arranged that the purest blood from the placenta is sent as quickly as possible to the head. To achieve this the liver is short-circuited by the ductus venosus, and the blood entering the right auricle is directed by the Eustachian valve through the foramen ovale into the left auricle. In this process the limbic bands of the auricle assist by drawing the inferior vena cava towards the foramen. From this point the adult course of the circulation is followed to the head. The returning stream enters the heart by the superior vena cava, and passes down into the right ventricle, being largely shut off from the other stream in the right auricle by the Eustachian valve and the limbic bands. It leaves the right auricle by the pulmonary artery, but as it is unnecessary for all this volume of blood to go to the lungs, it is diverted by the ductus arteriosus into the aorta beyond the origin of the carotids.

It is not correct to attribute the child's first breath to the stimulating effect of exposure to the lower temperature of the outside world, for interference with the placental circulation while the child is still *in utero* will cause it to breathe; and if the child be received into a bath at body temperature, respiratory movements will occur as usual. When oxygenation in the placental circulation is interfered with, carbon dioxide accumulates in the respiratory centre, and produces its usual effect—a stimulus to respiratory movements.

These respiratory movements aspirate a large

volume of blood into the lungs, which is then returned by the pulmonary veins to the left auricle. A fall of pressure, therefore, occurs in the right auricle, and a rise of pressure in the left, which helps to close the oblique opening in the foramen ovale. The downward movement of the diaphragm alters the plane in which the limbic bands act, so that they no longer draw the inferior vena cava towards the foramen ovale.

The alterations in pressure also help to close the ductus arteriosus, since the aorta now bulging outwards projects within its lumen, thus blocking the flow through it.

In this way the ordinary post-natal condition is arrived at. But if there be stenosis of the pulmonary valves, the mechanism of this change is fundamentally disturbed, though the foetal circulation will not have been embarrassed in any way. The pressure on the right side of the heart will be too great to allow of closure of the septum between the two sides, so that it remains patent either in its auricular or its ventricular portions. In the latter case there is probably a true congenital defect, a reversion to the type of reptilian heart; while the former is commonly the necessary result of a foetal endocarditis.

The deficiency in the exit of blood from the right ventricle will be made good to some extent by the ductus arteriosus remaining open. I have seen complete atresia of the pulmonary valves, in which the whole of the blood to the lungs reached them by this route.

Now, mere patency of the ductus arteriosus will not cause cyanosis; neither will simple intermixture of the arterial and venous streams through imperfections in the septum cause it. In a case recorded by Young there was only a trace of an interventricular septum, and yet there was no cyanosis until the heart began to fail. Morison's analysis of seventy-five cases shows that obstruction in the pulmonary artery is the lesion most commonly associated with cyanosis, and with this Coats agrees. If sufficient blood cannot enter the lungs, cyanosis is inevitable. That such blood as does go to the lungs is adequately oxygenated is shown by the striking failure of oxygen inhalations to benefit the cyanosis in any way. So long as there is free admission of blood to the lungs, cyanosis does not occur, even though there is an intermixture of the streams.

The only way in which the body can compensate for this is by charging the blood more highly with corpuscles, so that the oxygen capacity of that portion which does reach the lungs will be increased. Polycythæmia is therefore always met with in such cases, and may amount to 8,000,000 or 9,000,000 per cubic millimetre.

It has been contended that the polycythæmia and cyanosis are alike due to general congestion of the venous system from obstruction; but it has probably been the lot of everyone, as it certainly has been mine, to see cases of congenital heart disease with marked cyanosis and a high degree of polycythæmia,

in which signs of back - pressure were entirely lacking.

Other causes of chronic cyanosis call for only brief consideration. The other cardiac lesions typically associated with cyanosis are diseases of the tricuspid valve and adherent pericardium. Here the distribution to the lungs is at fault, so that oxygenation is imperfect; at the same time the back-pressure causes a certain degree of stasis in the capillaries, so that the blood there is richer in corpuscles than normal. If œdema be present also, this will increase the concentration of the blood. In this way a moderate degree of polycythæmia is found in the blood obtained from the peripheral circulation. This is spoken of as a relative polycythmæia, since there is not an absolute increase in the number of corpuscles, but only an alteration in their distribution with respect to the fluid constituents.

Mediastinal inflammation and growths act in very much the same way, by interfering with the diastolic filling of the heart.

Of all pulmonary conditions, emphysema causes the highest degree of chronic cyanosis. According to Osler, cyanosis of an extreme grade is more common here than in any other affection, except congenital heart disease. 'So far as I know,' he says, 'it is the only disease in which a patient may be able to go about, and even to walk into the hospital or consulting-room, with a lividity of startling intensity. The contrast between the extreme cyanosis and the

comparative comfort of the patient is very striking. In other affections of the heart and lungs, associated with a similar degree of cyanosis, the patient is invariably in bed, and usually in a state of orthopnoea.' He goes on to make another exception in favour of toxic cyanosis.

In emphysema there is such a gradual diminution of the oxygenating surface of the lung that the discomfort to the patient is reduced to a minimum. There is only a moderate polycythæmia, however. After emphysema, fibroid change in the lung is, perhaps, the most important cause of marked chronic cyanosis. Here again it is the diminished surface available for respiratory interchange that is responsible.

When, in these conditions, the right heart begins to fail, cardiac causes for cyanosis are superadded, and the dyspnoea becomes marked. Until that point is reached the right heart has an extraordinary power, as we saw in Chapter IX., of compensating for increased resistance in the pulmonary circulation. Thus, in pneumonia, cyanosis is much more an evidence of failure of the right heart than of any increase in the consolidation.

I have never seen oxygen produce a more striking alleviation of cyanosis than in emphysema with failing heart. This contrasts remarkably with the total failure of such treatment in congenital heart disease, and provides a further argument against explaining the cyanosis in that condition as due to back-pressure.

Local cyanosis, such as occurs in Raynaud's disease and other vasomotor diseases, need not detain us. Traumatic cyanosis, which is seen in the rare condition of pressure stasis following severe crushes of the chest, has been shown by Beach to be due to mechanical over-distension of the veins and capillaries. True extravasations of blood may occur as well, however, especially in the lax tissues around the eye, where the ordinary changes of colour in bruises will follow.

Conclusions.—Toxic cyanosis is due to a chemical change in the hæmoglobin molecule, produced by drugs or intestinal intoxication, and leading to the formation of methæmoglobin or sulphæmoglobin. It is not associated with polycythæmia, and there may be marked oligocythæmia.

True cyanosis from diminished oxygen in the red corpuscle is typically associated with polycythæmia, which may be—

1. *Absolute* where there is simple failure of oxygenation, either—

(a) In the lungs, because some of the blood does not get there, as in congenital heart disease, or because there is reduction in the oxygenating area of the lungs, as in emphysema; or,

(b) In the tissues, because they are unable to take up oxygen so readily, as in erythræmia; or,

2. *Relative*, from anasarca, which causes concentration of the blood, as in failing heart, or in a heart

embarrassed by pericardial adhesions, which interfere with its filling.

I would emphasize, in conclusion, the assistance that the blood-count and the spectroscope will give in making the diagnosis on which correct treatment will be based.

CHAPTER XII

THE RÔLE OF CALCIUM IN THE BODY

THOUGH the data are inadequate as yet for a system of 'mineral physiology,' it is clearly recognised that the metallic salts play an important part both in the physiology and pathology of metabolism. Thus, retention of sodium chloride is known to be a factor in the production of œdema, and iron plays an essential part in the therapeutics of chlorosis. Indeed, we are constantly using metallic drugs, and modifying metabolism thereby, though it must be admitted that in many cases we lack precise information as to the way in which they act. Yet it might be expected that investigations on such points would be simpler to carry out, and more definite in their results, than those on the action of organic bodies of which the chemical composition is often not completely known.

How essential the salts are to the body is shown by Forster's experiments. He fed dogs on ash-free fats and carbohydrates, and meats which had been extracted with water. At the end of twenty-six to

thirty-six days the animals were moribund. Probably they might have lived longer if they had been deprived of food altogether, with the exception of water, since the metabolism of the abundant diet provided would aid in increasing the loss of salts from the body.

Lunin found that, whereas mice lived well on a diet of dried cow's milk, they died in twenty to thirty days if fed on the organic but ash-free constituents, together with the extracted salts of cow's milk. Apparently, some at least of the salts must be provided in organic combinations such as are found in plant or animal foods.

Calcium is the one metal of whose action in the body we have some definite knowledge, and the results it has yielded in therapeutics have been of striking interest. This is largely due to the ingenious experiments of Sir A. E. Wright, who has taken advantage of the ease with which it can be added to, or abstracted from, the diet.

In one sense, calcium may be regarded as a very inert substance, as it is one which is deposited in largest amounts in normal tissue, like bone, which has a very sluggish metabolism, or in any area of dead tissue which is not infected, and is so large or so situated that it cannot be absorbed. It is interesting to find that the percentage of calcium may be almost exactly the same in either case. Muscles showing the reaction of degeneration contain an excess of calcium salts, as do malignant tumours

which are undergoing retrogression. The ganglion cells of the brain which have become degenerated or necrotic, particularly in the neighbourhood of old hæmorrhages, become infiltrated with calcium salts until a complete cast is formed, with dendrites and axis cylinder infiltrated alike (Wells). Calcification in quiescent tuberculous masses is a condition familiar to everyone. The deposit of calcium in areas of fat necrosis, and in the adipocere formed in bodies buried in damp soil, illustrates the same thing.

The replacement of elastic tissues by calcareous material may be regarded as a characteristic feature of growing old, and is well seen in arterial degeneration, which is in a sense a form of premature senility.

Le Noir formulated the following 'law' of calcification: The organism has a tendency to rid itself of valueless or toxic compounds by depositing them in tissues which have been previously altered, or in which metabolism is least active, and calcium salts do not form an exception to this general rule. This, though perhaps a little fanciful, contains a germ of truth.

It might be urged that the part played by calcium in the clotting of blood—a change which signifies its death as a tissue—is another example of this law; but, as will be pointed out later, the calcium only renders the fibrin ferment active, and does not form an essential part in the resulting clot.

But all the activities of calcium cannot be disposed

of so summarily; for calcium salts are essential to the heart-beat, and indeed, if they were simply inert in the body, no bad result would follow their removal from the diet. But calcium is constantly leaving the body in the excretions, and it must be replaced. Not only is it excreted in the urine, but Voit found that it was also eliminated by the bowel in small amounts—about 0·15 to 0·16 gramme a day. Some authorities regard the excessive drain of calcium salts in diabetes as one of the factors in the production of acid intoxication. This all points to a really active function for these salts in metabolism.

Lime-salts are absorbed with difficulty, and appear to retard also the absorption of the fluid in which they are dissolved. The most striking effects of altering the calcium content of the diet are found in connection with the curdling of milk and the clotting of blood; these will therefore be dealt with first.

Calcium and the Curdling of Milk.—The curdling of milk takes place in two stages: first, the rennin of the gastric juice converts the caseinogen into soluble casein; then the calcium salts present precipitate the casein in a soluble form. If the calcium salts be removed, this precipitation does not occur.

Now, in the feeding of infants on cow's milk, one of the disadvantages is that the curd is tough and massive, quite unlike the much finer flocculi that are formed in human milk. As cow's milk is richer in proteins than human milk, this can be remedied to a certain extent by dilution; but in that case the carbo-

hydrates and fats are reduced too much, as is seen from the following table by Poynton :

	Human Milk.	Cow's Milk.		
		I. 1 of Milk to 2 of Water.	II. Equal Parts.	III. 2 of Milk to 1 of Water.
Proteins	1·5	1·0	1·5	2·0
Fats	3·5	1·3	2·0	2·8
Carbohydrates	6·5	1·6	2·5	3·3

Thus simple dilution may mean under-nutrition. This can be corrected by addition of sugar and cream, but the method is a little troublesome, and does not do away altogether with the objectionable production of a tough curd.

Cow's milk contains six times as much calcium as human milk, so if we can remove some of this we need not dilute the milk so much. Oxalates and fluorides, which were first used to precipitate calcium, are poisonous, and therefore cannot be employed here. Wright found that citrates, which are harmless, had a similar action. According to Martin, citrate of soda acts by forming a double salt with the calcium, which is not available for curdling of milk or clotting of blood. This has the additional advantage that the calcium is not removed entirely, so that it is still available for other purposes in metabolism.

If 3 grains of sodium citrate be added to each

ounce of milk, there is only a very fine curd ; and 2 grains, or even 1, will markedly diminish its cohesion. The sodium salt is more effective than the potassium salt. The method is very easily put into practice, for the salt is freely soluble, and the required amount can be prescribed in a drachm of water, to be put in each feed of milk. A little chloroform-water should be added to a bottle that has to last a week, since a growth of fungus may form in the dilute solution.

In such doses it scarcely alters the taste of the milk at all, and, as it is a neutral salt, it does not tend to inhibit gastric secretion as do the alkaline salts.

Poynton sums up the advantages of this treatment as follows : It renders the curd of cow's milk more easily digestible ; it is cheap, convenient to handle, easy to control, and progressive in principle. It allows the milk to be given in a more concentrated form, and thus avoids to some extent the risk of under-feeding ; there is no danger of scurvy ; it gains the confidence of the mother, who naturally believes in medicines. Besides employing it in dyspepsia, he uses it as a routine for weaning a healthy infant on to cow's milk, gradually diminishing the amount of citrate. He does not find it of value in the rare cases of complete intolerance of cow's milk, in severe cases of gastro-enteritis from impure milk, or in organic diseases, such as congenital hypertrophic stenosis of the pylorus. In the last case, however, I think it

may be a useful adjunct to other procedures, since, as we have seen, it is essential to prevent the formation of any lumps in the stomach.

It is called for whenever undigested curds appear in the stools. Apart from other reasons to be considered presently, it should be used in typhoid fever under such circumstances. Our treatment of this disease is often fallacious in that we regard too much the condition of the food when it enters the mouth, rather than its condition as it passes over the ulcers; it is clear that many solid foods are fluid by that time, while milk, though liquid when swallowed, will form curds that are irritating in the ileum.

The practical success of this method raises doubts as to the physiological advantages of curdling in general. It is usually claimed that, did curdling not occur, the milk would pass along the intestine too rapidly, and thus escape unabsorbed; but, as a matter of fact, we find that the milk may be absorbed more completely when it is thus prevented from curdling. Pancreatic juice contains a milk-curdling ferment, but if the juice be active no curd is seen, because the trypsin will digest it as fast as it forms. On the addition of 6 per cent. sodium chloride, tryptic activity is delayed, and obvious curdling occurs. Thus a regulating mechanism is provided, which will delay the onward passage of the milk should the pancreatic digestion be enfeebled, and strongly suggests that, as long as this is active, the formation of a curd has no particular advantage. At any rate, the fre-

quency with which I have seen tough cheesy masses in the stomachs of infants post-mortem has impressed me with the accompanying drawbacks.

Calcium and the Clotting of Blood.—In the clotting of blood, the part played by calcium is different. Physiologists regard fibrin ferment as resulting from the interaction of three substances—thrombogen in the plasma; thrombokinase contained in all tissue cells, including the leucocytes and platelets; and calcium salts. Once the ferment has been formed, the calcium can be removed without interfering with the clotting. Thus it operates at an earlier stage in this proceeding than in curdling.

Wright has observed the rate of coagulation by means of a capillary tube, into which the blood is drawn, and the time required for its clotting noted. In this way the effect of therapeutic measures can be controlled by a simple test. If coagulation be too quick, the blood can be decalcified by giving citrate of soda; if too slow, calcium salts can be added.

Indications for Decalcification.—Wright asserts that every adult patient who is placed upon a dietary of milk is thereby brought into a condition which predisposes to thrombosis, in consequence of the large intake of calcium salts. He believes this fact accounts for the frequency of thrombosis as a sequel of typhoid fever. F. J. Smith, also, is of opinion that the rarity with which thrombosis occurred in his series of cases of typhoid fever is due to his allowing them a more liberal and not exclusively milk diet.

In this connection it is of great interest to recall the special frequency with which thrombosis occurred as a sequel to typhoid fever in the South African War.* The usual explanation given of its frequency was that prolonged marching had thrown a strain on the veins of the leg. As thrombosis is such a late event in typhoid fever, one would imagine that this factor must have lost its effect during the long enforced rest that preceded the clotting. It seems to me much more likely that the general use of condensed milk played an important part. Fresh milk contains some citric acid, and thus provides the antidote to some of its abundant calcium. This citric acid is apt to separate out in an insoluble form from condensed milk.

Hæmatemesis from a gastric ulcer may be followed by thrombosis. Here, also, the milk diet may play a part.

In all cases where milk diet is used for some time the addition of citrate of soda should be ordered. It is such a simple procedure that it would justify itself if it saved one patient from the dangers, pain, and chances of lifelong inconvenience that are entailed by thrombosis. It is important to carry the treatment well into convalescence, as after a time decalcification

* About 6 per cent. of all cases developed thrombosis, or double the proportion of the cases which do so in this country. Crombie's oft-quoted figures in which 25 per cent. suffered from thrombosis are vitiated by the fact that many of his cases were those invalided home on account of this complication.

is followed by an increase in the calcium salts of the blood. This very probably depends upon the bringing into solution again of the calcium salts, which have been precipitated by citric acid, but not excreted.

When once clotting has occurred in a vein, the question arises whether it is better to give citrates with the view of aiding resolution, or calcium salts to assist in getting the clot as firm as possible and thus diminishing the risk of embolism. Practical experience is in favour of decalcification as soon as thrombosis takes place, for when clotting begins it may spread unless the coagulability of the blood is diminished. It has already been stated that fresh lemon-juice is believed by some to be more effective for this purpose than sodium citrate.

Indications for Increasing Coagulability. — Wright's attention was drawn to this subject by the fact that as a boy he was subject to attacks of aggravated giant urticaria when he took acid fruits, which are, of course, rich in decalcifying agents. Chilblains, 'angio-neurotic' oedema, and physiological albuminuria, he considers to be, like urticaria, due to a lowered coagulability of the blood, which allows of transudation of plasma from the vessels into the lymph spaces—a 'serous hæmorrhage,' as he calls it. The bearing of this on albuminuria has been referred to in Chapter V. The principle is the same in all these conditions: the blood must be replenished with those salts which render the plasma more coagulable and viscid.

For this purpose calcium lactate has yielded him the best results. This salt recommends itself for use, firstly, by the fact that it is devoid of unpleasant taste, is sufficiently soluble (about 1 in 10) in water, and is suitable for administration in the form of powders; and, secondly, by the fact that the salts of organic acids, and more particularly of lactic acid, are known to be readily oxidized in the body, with the result that their bases are placed more fully at the disposal of the organism than would be the case when the corresponding mineral acid salts are exhibited. A dose of 4 grammes (1 drachm) may increase the coagulability of the blood within twenty minutes, and maintain its effect for from four to seventeen days. It should be used whenever it is desired to exalt coagulability as rapidly as possible. When the object is to maintain a permanently high level of blood coagulability, the dosage should be 1 gramme (15 grains) three times a day.

Magnesium salts have been shown to bring about a similar change, which explains the rationale of magnesium carbonate in the treatment of urticaria, and its special efficacy in that form of urticaria which follows upon the ingestion of decalcifying agents.

Calcium salts are used with the intention of promoting clotting in the sac of an aneurysm, in purpura, hæmophilia, intestinal hæmorrhage, and as a precautionary measure against bleeding during operations. Cushny doubts whether any improvement observed in such cases can really be referred to the

drug, since much more calcium is taken in with the food than is sufficient for the body, and the pharmacopœial salts are not more easily absorbed than the combinations present in food. The fact, however, that the coagulation-time can be diminished thus, even when the intake of calcium in the food is adequate, suggests that some of the benefits recorded may fairly be attributed to the drug.

G. W. Ross met with the association of severe chronic headache and a troublesome urticaria with deficient coagulability of the blood in a patient. Calcium chloride was given for the urticaria, and the headaches vanished also. This suggested to him that the headache might also be due to a similar 'serous hæmorrhage' into the meninges. He treated forty-eight cases with 15 grains of the chloride or the lactate of calcium three times a day. Forty of the cases obtained complete relief and eight considerable relief. With the relief, the coagulability of the blood was exalted in all the cases in which it was tested. According to him the type of headache which responds to this treatment presents the following characteristics :

1. It is present and most severe on waking, and tends to disappear one to six hours later.

2. It is usually a dull, heavy ache or a frontal or temporal throbbing; occipital, vertical, or unilateral pain being less common.

3. This symptom is very chronic, often of several years' duration, and most intractable to ordinary treatment.

The type of patient who is the subject of such attacks he describes as follows: Women are more frequently affected than men. The expression is heavy and listless, the face is full, and the eyes are often puffy. Some anæmia is usual; constipation is the rule; loss of appetite and indigestion are common. There is a tendency to chilblains, urticaria, and œdema, the latter manifesting itself more commonly as a morning fulness between the eyes, and less frequently as an œdema of the ankles and feet. The patient sleeps heavily, but wakes without feeling rested, and there is a tendency to mental depression. Irritability combined with languor he regards as characteristic.

He obtained an interesting confirmation of his views by finding the symptoms returned on the decalcification of the blood by giving sodium citrate, to disappear a second time on treatment with calcium lactate.

This line of treatment has not been very successful in hæmophilia, and it is accordingly interesting that Wright found in this disease that the coagulation of the blood may be quite uninfluenced by calcium salts given by the mouth, while it may be conspicuously increased by hypodermic injection of a suitable calcium salt. He therefore regarded a constitutional incapacity in the matter of the absorption of calcium salts as at least a factor in the situation. Unfortunately, hypodermic injection of calcium chloride is not free from risk, and Wright regards a 1 in 20 solution as the

maximum concentration of the lactate that can be safely injected.

Calcium and the Rhythm of the Heart.—In Chapter IX. it was shown that calcium salts were essential to the systole of the heart. Howell and Duke, in some recent experiments on this subject, found that increase in the concentration of calcium salts acted like stimulation of the accelerator nerve. There was augmentation of the beat chiefly, and with small doses augmentation only. A reduction in the calcium salts caused a more rapid as well as a more feeble beat. Loeb does not believe that calcium is really necessary for rhythmic activity, but that it and potassium neutralize the poisonous effects of sodium. In support of this he instances the case of a small fish, *fundulus* by name, which lives in salt water. It can be transferred to distilled water without injury, but if it be put in sodium chloride solution of the same strength as sea-water it dies. Apparently, sodium is poisonous unless it is antagonized by some other constituents of sea-water, the responsible constituents being the calcium and potassium, as it is sufficient to add them to the sodium chloride solution for the fish to be able to live as well as in sea-water. This experiment cannot, however, be accepted as a complete explanation of the rôle of calcium in cardiac rhythm. For instance, it does not explain why, if potassium be omitted, the heart stops in systole; while, if the calcium be left out, the arrest is always in diastole. Apparently, then, there must be an

antagonism between these two antidotes to sodium, which would be very difficult to understand.

This activity of calcium has not proved capable of any striking therapeutical application. It has been used as a heart tonic in pneumonia ; but, so far from being an invariable success, it has sometimes been followed by thrombosis—not an uncommon accident in this disease. We must remember that in acute infections ‘heart failure’ is often essentially a vaso-motor paralysis ; and in all cases calcium proves itself a two-edged sword in the treatment of circulatory failure, by reason of its liability to provoke clotting.

Calcium Salts and Rickets.—It may be stated, as a general rule, that deficiency of lime in the food affects the young more than adults, since the former require more for the forming of the skeleton. Young dogs fed on a diet poor in calcium fall into a condition resembling rickets, owing to deficient growth of the bones. Pigeons thus dieted exhibit fragility and atrophy of the bones. It might be expected, therefore, that the administration of calcium salts would be of decided benefit to rickety children. Such is not the case, however. There is no lack of lime in the blood in rickets, but from some cause the power of taking it thence and depositing it in the bones is diminished. Lime starvation, therefore, merely causes an imitation of rickets, because the bone cells, though still ready to deposit calcium, cannot obtain it.

Calcium and the Puerperal State.—During pregnancy

the blood has a brief coagulation-time, probably because it is rich in nutrient matters, including calcium salts, required for the growth of the foetus. Winckel finds that it has a somewhat diminished alkalinity, which would enable it to hold a larger amount of calcium salts in solution.

It is generally agreed that immediately after delivery the coagulation-time is below normal, though Hingston Fox thinks that it is not reduced to the extent which others have supposed. As suckling begins, the coagulation-time naturally increases perceptibly from the drainage of calcium salts into the milk. Fox suggests that an observation of the coagulation-time of the blood after delivery might give timely warning of the risk of thrombosis or embolism if it were quick, or of post-partum hæmorrhage if it were slow. Appropriate treatment, with citric acid on the one hand, or with calcium lactate on the other, would help to rectify the condition.

The part played by ovarian activity in the metabolism of calcium is probably considerable, but it still awaits complete elucidation. The benefits sometimes seen after removal of the ovaries in osteomalacia may depend on this, for the calcium loss in the urine is then replaced by a marked retention. This improvement is sometimes only temporary, but it is very interesting in view of Blair Bell's observation of the abundant presence of calcium salts in the systems of pregnant women, where the menstrual function is naturally in abeyance.

Many of the other therapeutical applications of calcium salts depend either on their physical state—as, for instance, the use of chalk as an astringent—or on their alkalinity, and do not, therefore, concern us here. The usefulness of a decalcifying agent in oxaluria has already been explained (see p. 144).

The Allied Metals, Barium and Strontium.—Barium is the most poisonous metal of the group. It is very slowly absorbed from the bowel, and may excite vomiting and purging, with very active peristalsis. It is incapable of replacing calcium in its relations to living matter, and is not nearly so efficient in maintaining the rhythm of the excised heart. According to some observers, it can replace calcium to a limited extent in the coagulation of the blood. It has been used principally for its effect on the cardio-vascular system. The waters of Llangammarch Wells owe their reputation in the treatment of heart disease largely to the barium they contain. Like digitalis, barium causes the frog's heart to beat more slowly, but more strongly, and it produces a great rise of blood-pressure by constriction of the blood-vessels. As the action is, apparently, directly upon the muscle fibres, I have used this drug in conditions of vasomotor paralysis, where it is useless to stimulate the exhausted or intoxicated nervous system further.

Strontium is the least poisonous of the three, being comparatively inert, even when injected directly into the blood. Like the others, it is absorbed very

slowly from the bowel. It can replace calcium more or less perfectly in its influence on the heart-beat. It has been used chiefly for its anion, in the form of strontium bromide, for epilepsy; but, as it is absorbed so much more slowly than the corresponding salts of sodium or potassium, it is really much less satisfactory for this purpose.

Antagonism of Calcium to Magnesium.—Although magnesium salts, like calcium salts, according to Wright, can exalt the coagulability of the blood in appropriate doses, these two metals are generally antagonistic in their effect on the tissues. The striking observations of Meltzer and Auer on this point deserve attention, although they are not yet capable of therapeutical application. The intracerebral instillation of two or three drops of a solution of magnesium sulphate produced a peculiar paralysis in rabbits, while injection of other salts was either indifferent or caused convulsions. The subcutaneous or intravenous injection of magnesium salts caused a general anæsthesia with paralysis, in which the reflexes were abolished and the blood-pressure was lowered. When the dose exceeded the point of safety, respiration ceased, the heart usually continuing to beat for some time longer. But as long as there were some efficient heart-beats and a few respiratory gasps, the intravenous injection of a calcium salt, such as the chloride or the acetate, infallibly improved the respiration at once, and quickly revived the animal.

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Magnesium favours inhibitory processes in the body, and in this it is definitely antagonized by calcium. All this emphasizes the conclusion reached by the study of mineral physiology, that the normal qualities, especially the irritability of animal tissues, depend upon their containing sodium, potassium, calcium, and magnesium ions in their *right proportions*.

PRINCIPAL REFERENCES

CHAPTER I

- BATTY SHAW : *Organotherapy*. Cassell and Co., 1905.
STARLING : *Croonian Lectures*, Royal College of Physicians.
Lancet, 1905, vol. ii., pp. 339, 423, 501, 579.
SWALE VINCENT : *Lancet*, 1906, vol. ii., p. 348.

Thyroid Gland.

- EDMUNDS : *Lancet*, 1908, vol. i., p. 227.
FORSYTH : *Quarterly Journal of Medicine*, vol. i., pp. 150, 287
MACKENZIE, H. W. G. : *Clinical Journal*, October 30, 1907, p. 33.
MURRAY, G. R. : *Lancet*, 1904, vol. ii., p. 583.

Suprarenal Capsules.

- ELLIOTT, T. R. : *Journal of Physiology*, vol. xxxii., p. 401.
GRUNBAUM, O. F. F. : *The Practitioner*, 1907, vol. lxxix., p. 211.
LANG, B. T. : *St. Bartholomew's Hospital Journal*, January, 1908, p. 55.
LANGLEY, J. N. : *Journal of Physiology*, vol. xxvii., p. 237.
PLANT AND STEELE : *British Medical Journal*, 1905, vol. ii., p. 125.
SCHAFER : *Lancet*, 1908, vol. i., pp. 1531, 1606.

Thymus.

- DUDGEON, L. S. : *Transactions of the Pathological Society*, vol. lv., p. 151.
HENDERSON : *Journal of Physiology*, vol. xxxi., p. 222.
PATON : *Journal of Physiology*, vol. xxxii., p. 28.
PATON AND GOODALL : *Journal of Physiology*, vol. xxxi., p. 49.
PHILLIPS, S. : *Clinical Journal*, February 12, 1908, p. 285.

CHAPTER II

EDKINS : *Journal of Physiology*, vol. xxxiv., p. 133.

PAWLOW : *The Work of the Digestive Glands*. Translated by W. H. Thompson. Griffin and Co., 1902.

STARLING : *Recent Advances in the Physiology of Digestion*.

Achlorhydria and Hyperchlorhydria.

BROADBENT, W. : *Lancet*, 1904, vol. i., p. 867.

KAUFMANN : *American Journal of the Medical Sciences*, vol. cxxxv., p. 207.

MILLER AND WILLCOX : *Lancet*, 1907, vol. ii., p. 1670.

MOORE, B., and others : *Lancet*, 1905, vol. i., p. 1120.

ROBERTS, SIR W. : *Diet and Digestion*. Smith, Elder and Co., 1891.

WILLCOX : *Lancet*, 1905, vol. i., p. 1566 ; *ibid.*, 1908, vol. ii., p. 220.

WILLIAMS, LEONARD : *Minor Maladies*. Baillière, Tindall and Cox.

Rectal Feeding, etc.

GRAVEN-MOORE : *Practitioner*, 1907, vol. lxxix., p. 668.

LAMBERT : *The Lenhartz Treatment of Gastric Ulcer*. *American Journal of the Medical Sciences*, January, 1908, vol. cxxxv., p. 18.

SHARKEY : *Lancet*, 1906, vol. ii., p. 1263.

Gastro-jejunosomy ; Perigastric Adhesions, etc.

CAMERON, H. C. : *British Medical Journal*, 1908, vol. i., p. 140.

PATERSON, H. J. : *Lancet*, 1907, vol. ii., p. 815.

PATON, E. P. : *Lancet*, 1904, vol. i., p. 357.

Congenital Hypertrophic Stenosis of the Pylorus.

CAUTLEY : *Transactions of the Royal Medical and Chirurgical Society*, November, 1898, vol. lxxxii., p. 41.

STILL : *Lancet*, 1905, vol. i., p. 632 ; *Transactions of the Pathological Society*, vol. l., p. 86.

CHAPTER III

BAINBRIDGE, F. A. : *Journal of Physiology*, vol. xxxi., p. 98 ; *Bio-Chemical Journal*, vol. iii., p. 82.

BAINBRIDGE AND BEDDARD : *Bio-Chemical Journal*, vol. i., p. 429.

- BAYLISS AND STARLING: Proceedings of Royal Society, 1902, vol. lxi., p. 352; Croonian Lecture, Royal Society, 1904; Journal of Physiology, 1902, vol. xxviii., p. 325; 1903, vol. xxx., p. 61; 1905, vol. xxxii., p. 129.
- BYROM BRAMWELL: Scottish Medical Journal, 1904, vol. xiv., p. 321; Clinical Studies, 1904, vol. ii., part iv., p. 348.
- CAMMIDGE: Arris and Gale Lecture, Lancet, 1904, vol. i., p. 782; Clinical Journal, April 1, 1908, p. 392.
- CATHCART: Journal of Physiology, 1904, vol. xxxi., p. 497.
- COHNHEIM, O.: Zeitschr. f. physiol. Chemie, 1903, vol. xxxix., p. 386.
- CROFTAN, A. C.: New York Medical Journal, vol. lxxix., p. 882.
- DALE, H. H.: Philosophical Transactions, 1905, B. cxcvii., p. 25.
- HAM AND CLELAND: Lancet, 1904, vol. i., pp. 1378 and 1684.
- LANGDON-DOWN: Clinical Society's Transactions, 1869, vol. ii., p. 119.
- MAYO ROBSON: Hunterian Lectures, Lancet, 1904, vol. i., pp. 773, 845, 911.
- MAYO ROBSON AND CAMMIDGE: Surgery and Pathology of the Pancreas. Saunders, 1908.
- NOEL PATON: Journal of Physiology, 1904, vol. xxxii., p. 59.
- OPIE, E. L.: Disease of the Pancreas. Philadelphia, 1908.
- PAWLOW: The Work of the Digestive Glands. Translated by W. H. Thompson. Griffin, 1902.
- PLIMMER, R. H. A.: Journal of Physiology, vol. xxxiv., p. 93.
- RENNIE AND FRASER: Bio-Chemical Journal, vol. ii., p. 7.
- STARLING: Transactions of the Pathological Society, 1903, vol. liv., p. 255; Recent Advances in the Physiology of Digestion, 1906.
- TUCKETT: Journal of Physiology, 1899, vol. xxv., p. 63.
- VERNON, H. M.: Journal of Physiology, 1901, vol. xxvi., p. 405; 1904, vol. xxxi., p. 346.
- VON NOORDEN: Article on Diabetes, Twentieth-Century Practice of Medicine, vol. ii., p. 33.

CHAPTER IV

- AUSTEN : Journal of Medical Research, vol. xvi., p. 71.
MACLEOD : Recent Advances in Physiology and Bio-Chemistry.
edited by Leonard Hill, p. 387. Arnold.
STOOKEY : Journal of Medical Research, vol. xv., p. 322.
WALKER HALL : Purin Bodies. Sherratt and Hughes, 1903.

CHAPTER V

Oxaluria.

- VON NOORDEN : Metabolism and Practical Medicine, vol. iii.,
p. 1046. Heinemann.

Phosphaturia.

- JOULIE : See Leonard Williams, Clinical Journal, April 18, 1906.
RALFE : Clifford Allbutt's System of Medicine, vol. iii., p. 253.
VON NOORDEN : Metabolism and Practical Medicine, vol. iii.,
p. 1055.

Albuminuria.

- CHITTENDEN : Physiological Economy in Nutrition. New York,
1904.
D'ARCY POWER : St. Bartholomew's Hospital Reports, vol. xxiii.,
p. 173.
DUKES : Lancet, 1891, vol. ii., p. 1327 ; *ibid.*, 1907, vol. ii.,
p. 514.
HINGSTON FOX : Lancet, 1906, vol. ii., p. 497.
VON NOORDEN : Metabolism and Practical Medicine, vol. ii., p. 433.
WRIGHT, SIR A. E. AND ROSS, G. W. : Lancet, 1905, vol. ii.,
p. 1164.

CHAPTER VI

- BEDDARD : Practitioner, 1907, vol. lxxix., p. 95.
HALLIBURTON : Practitioner, 1907, vol. lxxix., p. 1.
NOEL PATON : Journal of Physiology, vol. xxxii., p. 59.
OPIE, E. L. : Diseases of the Pancreas. 1903.
PAVY : Clinical Journal, November 13, 1907, p. 78.
ROSE BRADFORD : Practitioner, 1907, vol. lxxix. p. 13.

- STUART HART: *Medical Record*, 1907, vol. lxxii., p. 518.
 VON NOORDEN: *Metabolism and Practical Medicine*, vol. iii.,
 p. 527.

CHAPTER VII

- BAINBRIDGE: Arris and Gale Lecture on Acid Intoxication,
Lancet, 1908, vol. i., p. 911; *St. Bartholomew's Hospital
 Journal*, July, 1908, p. 148.
 BALDWIN: *American Journal of the Medical Sciences*, 1905,
 vol. cxxx., p. 649.
 BATTY SHAW AND TRIBE: *British Medical Journal*, 1905, vol. i.,
 p. 347 (which see for bibliography of recurrent vomiting in
 children).
 BEDDARD: *Lancet*, 1908, vol. i., p. 782.
 BEDDARD AND SPRIGGS: *Proceedings of British Medical Associa-
 tion*, *Lancet*, 1904, vol. ii., p. 405.
 BEDDARD, PEMBREY, AND SPRIGGS: *Journal of Physiology*,
 vol. xxxi.; *Proceedings of the Physiological Society*,
 June 18, 1904.
 CARMICHAEL AND BEATTIE: *Lancet*, 1905, vol. ii., p. 437.
 Discussion at Society of Anæsthetists, *Lancet*, 1907, vol. i.,
 p. 438.
 EDE AND WHITLEY: *Bio-Chemical Journal*, 1906, vol. i.,
 p. 11.
 GARROD: *St. Bartholomew's Hospital Journal*, January, 1907,
 p. 58.
 GEE: *St. Bartholomew's Hospital Reports*, vol. xviii., p. 1.
 GUTHRIE: *Lancet*, 1894, vol. i., pp. 193 and 257; 1903, vol. ii.,
 p. 10; 1905, vol. ii., p. 588.
 HUBBARD: *Boston Medical and Surgical Journal*, 1905, vol. clii.,
 p. 744.
 LEATHES: *Problems in Animal Metabolism*, pp. 90, 109, 119;
Acidosis in Pregnancy, *Proceedings of the Royal Society of
 Medicine*, 1908.
 LONGRIDGE: *Lancet*, 1905, vol. ii., p. 1405.
 SCHRYVER: *Bio-Chemical Journal*, 1906, vol. i., p. 123.
 TELFORD AND FALCONER: *Lancet*, 1906, vol. ii., p. 1341 (which
 see for bibliography of delayed chloroform-poisoning).

338 PHYSIOLOGICAL PRINCIPLES

VON NOORDEN and MOHR: Disorders of Metabolism and Nutrition, part iv., Acid Auto-intoxication. Wright.

WHITRIDGE WILLIAMS: Lancet, 1905, vol. ii., p. 1172.

CHAPTER VIII

GARBOD: Transactions of the Pathological Society, 1904, vol. lv., p. 142; Quarterly Journal of Medicine, vol. i., p. 207.

GIBSON, G. A., Quarterly Journal of Medicine, vol. i., p. 29.

HAMILTON: Aberdeen University Studies, 1906, No. 21, p. 1.

HERTER: New York Medical Journal, 1898, vol. lxxviii., pp. 89, 116.

HORDER: St. Bartholomew's Hospital Journal, February, 1908. p. 66.

METCHNIKOFF: The Prolongation of Life. Heinemann.

STRANGWAYS AND BURT: Bulletin of the Committee for the Study of Special Diseases, Cambridge, 1907, vol. i., p. 75.

TAYLOR: Osler's System of Medicine, vol. i., p. 270.

WELLS: Chemical Pathology, pp. 157 and 464. Saunders, 1907.

WEST AND WOOD CLARKE: Lancet, 1907, vol. i., p. 272.

WOOD CLARKE AND HURTLEY: Journal of Physiology, vol. xxxvi., p. 62.

CHAPTER IX

ASCHOFF: British Medical Journal, 1906, vol. ii., p. 1103.

BARR: British Medical Journal, 1906, vol. ii., p. 1122.

CARLSON: American Journal of Physiology, vols. xii., xiii., xiv., xv., xvi.

ERLANGER: Journal of Experimental Medicine, 1906, vol. viii., p. 8; British Medical Journal, 1906, vol. ii., p. 1111.

GASKELL: Schafer's Physiology, vol. ii., p. 169.

GIBSON, A. G.: Quarterly Journal of Medicine, vol. i., pp. 173, 182.

GIBSON, G. A.: British Medical Journal, 1906, vol. ii., p. 1113.

HANDFORD: British Medical Journal, 1904, vol. ii., p. 1745.

HAY: British Medical Journal, 1905, vol. ii., p. 1084.

- HAY AND MOORE: *Lancet*, 1906, vol. ii., p. 1271.
HERING: *Pflüger's Archiv*, Bd. cxvi., p. 143.
JELLYCK, COOPER, AND OPHULS: *Journal of the American Medical Association*, 1906, vol. xlv., p. 955.
KEITH AND FLACK: *Journal of Anatomy and Physiology*, vol. xli., p. 172.
KEITH AND MILLER: *Lancet*, 1906, vol. ii., p. 1429.
LUCE: *Deutsch. Arch. f. Klin. Med.*, 1902, Bd. lxxiv., p. 370.
MACKENZIE: *The Study of the Pulse*, Pentland, 1902; *British Medical Journal*, 1906, vol. ii., p. 1107; *Quarterly Journal of Medicine*, vol. i., pp. 39, 181, 481.
ROHDE: *Arch. für Experimentelle Pathologie und Pharmacologie*, 1905, vol. lxiv., p. 104.
SCHMOLL: *Deutsch. Arch. f. Klin. Med.*, 1906, Bd. lxxxvii., p. 554.
STENGEL: *American Journal of Medical Sciences*, 1905, vol. cxxx., p. 1088.

CHAPTER X

- BRODIE AND DIXON: *Journal of Physiology*, vol. xxx., p. 476.
CLIFFORD ALLBUTT: *British Medical Journal*, 1906, vol. ii., p. 1004.
CUSHING: *Johns Hopkins Hospital Bulletin*, vol. xii., No. 126, p. 290, September, 1901.
DIXON: *Proceedings of the Royal Society of Medicine*, vol. i., Therapeutical and Pharmacological Section, p. 38.
GASKELL: *Journal of Physiology*, vol. iii., p. 62.
GULLAND: *British Medical Journal*, 1898, vol. ii., p. 781.
JANEWAY: *Clinical Study of Blood-Pressure*. Appletons, 1904.
LEONARD HILL: *The Physiology and Pathology of the Cerebral Circulation*. Churchill, 1896.
LEONARD WILLIAMS: *Clinical Journal*, October 2, 1907, p. 396; *ibid.*, January 8, 1908, p. 197; *Lancet*, 1907, vol. ii., p. 1606; *The Hospital*, December 14, 1907.
LOCKHART MUMMERY: *Lancet*, 1905, vol. i., pp. 696, 776, 846.
MACKENZIE: *British Medical Journal*, 1906, vol. ii., p. 1007.
MORISON: *Edinburgh Medical Journal*, 1898, vol. iv., New Series, p. 413.

340 PHYSIOLOGICAL PRINCIPLES

RUSSELL, W.: Arterial Hypertonus, Sclerosis, and Blood-Pressure. Green, 1907.

SAVILL, T. D.: Transactions of the Pathological Society, 1904, vol. lv., p. 875.

CHAPTER XI

LANE JOYNT: Lancet, 1905, vol. i., p. 856.

MORISON: Practitioner, vol. xl., pp. 101, 179.

OSLER: American Journal of the Medical Sciences, 1903, vol. cxxvi., p. 187; Lancet, 1908, vol. i., p. 143.

PARKES WEBER: Transactions of the Royal Medical and Chirurgical Society, 1905, vol. lxxxviii., pp. 191-223.

SAUNDBY AND RUSSELL: Lancet, 1902, vol. i., p. 515.

YOUNG: Journal of Anatomy and Physiology, 1907, vol. xli., p. 190.

CHAPTER XII

BLAIR BELL: British Medical Journal, 1907, vol. i., p. 921.

HINGSTON FOX: Lancet, 1908, vol. i., p. 99.

HOWELL: Text-book of Physiology, pp. 429, 520, 716. Saunders, 1907.

HOWELL AND DUKE: Journal of Physiology, vol. xxxv., p. 131.

MELTZER AND AUER: American Journal of Physiology, vol. xxi., p. 400.

POYNTON: Lancet, 1904, vol. ii., p. 433.

ROSS, G. W.: Lancet, 1906, vol. i., p. 143.

SMITH, F. J.: British Medical Journal, 1906, vol. ii., p. 1015.

WELLS: Chemical Pathology, pp. 364-374.

WRIGHT, Sir A. E., AND PARAMORE, W. E.: Lancet, 1905, vol. ii., p. 1096.

INDEX

A

ACETONE, 180, 181, 188; tests for, 189; precursors of, 190

Acetonuria, 188; broncho-pneumonia and, 202; carbohydrates and, 190; defective oxidation and, 192; in diabetes, 190, 197, 208; fatty diet and, 191; gastro-intestinal disorders and, 199; pernicious vomiting of pregnancy and, 199; post-anæsthetic, 202; recurrent vomiting and, 197; starvation and, 192; symptoms of, 197

Achlorhydria, 56, 58; acids in, 61; alkalies in, 60, 63; malignant disease and, 56; meat extracts in, 63; treatment of, 60

Acid intoxication, 194

Acid of gastric juice, 55; estimation of, 88

Acidol, 62

Acidosis, 194

Acids in achlorhydria, 61

Acromegaly, 42

Addison's disease, 27; blood-pressure in, 293

Adrenalin, 16; action of, 16; Addison's disease and, 28; in ascites, 24; bloodvessels and, 19; in cerebral hæmorrhage, 23; composition of, 16; deleterious effects of, 31; in hæmatemesis, 18; in hæmophilia, 23; in hæmoptysis, 22; in hæmorrhoids, 25; in heart failure, 19; in intestinal bleeding, 19; in local anaesthesia, 25; nasal mucous membrane and,

25; in ophthalmic surgery, 24; in pleural effusion, 24; in poisoning, 19; in shock, 21; in spinal anæsthesia, 26; in urinary disease, 25; in vomiting, 18

Albuminuria, 149; functional, 150; glycosuria and, 182; organic, 157

Alkaptonuria, 170

Antithyroidin, 14

Antitrypsin, 96, 119

Arthritis, chronic, and intestinal intoxications, 235

Asthma and the vasomotor system, 283

Auriculo-ventricular bundle, 243

Autolysis, 195

B

Barium salts, 292, 330

Bitters, value of, 54

Blood-pressure, 285; in acute infections, 21, 291; in Addison's disease, 29, 293; in albuminuria, 293; in aneurysm, 287; in cerebral hæmorrhage, 278, 292; in cerebral thrombosis, 292; elasticity of vessels and, 287, 290; estimation of, 289; influence of heart-beat on, 285; old age and, 299; peripheral resistance and, 286; in pneumonia, 293; in shock, 291; toxic rise of, 294, 298; in typhoid fever, 292; volume of blood and, 288

Brain and vasomotor system, 276

C

- Caffein in heart-block, 252, 264 ;
in nephritis, 164
Calcification, 316
Calcium salts, albuminuria and,
152 ; antagonism to magnesium
salts, 331 ; antagonism to
potassium salts, 327 ; beat of
heart and, 248, 317 ; clotting
of blood and, 321 ; curdling of
milk and, 317 ; headache and,
325 ; puerperal state and, 329 ;
rickets and, 328 ; serous exu-
dates and, 323
Cancer and hydrochloric acid, 56 ;
and trypsin, 112
Cardiac rhythm, disturbances of,
250 ; nature of, 242, 247, 249
Cell islets of pancreas, 106
Cerebral circulation, 276
Cerebral hæmorrhage and adren-
alin, 23 ; and blood-pressure,
278, 292, 293
Cerebral thrombosis and blood-
pressure, 292
Chloroform - poisoning, delayed,
202, 212
Cirrhosis of liver and intestinal
intoxications, 234
Citrates in acidosis, 187, 209 ; in
infant feeding, 319 ; in oxal-
uria, 144 ; in thrombosis, 322 ;
in typhoid fever, 320
Coma, diabetic, 209
Compensation in heart disease,
265
Congenital heart disease, 306
Congenital hypertrophic stenosis
of pylorus, 83
Cyanosis, 300 ; causes of, 310 ;
congenital heart disease and,
306 ; emphysema and, 310 ;
microbic, 229 ; polycythæmia
and, 301 ; toxic, 301 ; trau-
matic, 312

D

- Decalcification, indications for,
321
Delayed chloroform - poisoning,
202, 212

- Depressor nerves, 272, 284
Diabetes, 100, 177 ; acetonuria
and, 190, 197, 208
Diabetic puncture, 173
Diacetic acid, 180, 181, 188 ; pre-
cursors of, 190 ; tests for,
189
Diastolic filling of heart, 267
Diet in achlorhydria, 63 ; in dia-
betes, 184 ; in Graves' disease,
15 ; in hyperchlorhydria, 65 ;
in nephritis, 161
Digitalis in arterio-sclerosis, 255 ;
as a diuretic, 165 ; irregular
hearts and, 262 ; in mitral
stenosis, 255, 263
Diuretics, 163
Dyspepsia, 55 ; asthenic and
sthenic, 58

E

- Elasticity of vessels and blood-
pressure, 287, 290
Enterokinase, 95
Erepsin, 97
Erythæmia, 302
Extra-systoles, 256

F

- Fat necrosis, 98
Field of cardiac response, 258
Fœtal extract, 35

G

- Gastric contents, examination of,
88
Gastric digestion, 44 ; chemical
factor in, 46 ; diet and, 46, 51 ;
nervous factor in, 44 ; personal
equation in, 49 ; vagus and,
45
Gastric ulcer, 66
Gastritis, types of chronic, 56
Gastro - intestinal intoxication,
types of, 215
Gastro - jejunostomy, results of,
76
Gastrostaxis, 66
Gastrostomy, after-treatment of,
54
Graves' disease, 12

Glycosuria, 169; adrenalin and, 31, 175; albuminuria and, 182; detection of, 172; experimental, 173; iodothylin and, 7, 175; life insurance and, 179; pancreatic, 103, 176; physiological, 172; test diet in, 185; treatment of, 183; types of, 180

Glycuronic acid, 169

H

Hæmatemesis, treatment of, 67

Hæmatoporphyrinuria, 232

Hæmoptysis, treatment of, 22, 280

Heart, blood-pressure and, 285; disturbed rhythm of, 250; rhythm of, 242, 247-249; vasomotor system and, 284

Heart-block, 243, 246, 250; caffeine in, 252, 264; strychnine in, 252, 264; thyroid extract in, 264

Hormones, application of, 6; definition of, 3; general features of, 5; list of, 3

Horse serum in treatment of gastric ulcer, 75

Hyperchlorhydria, 55; diet in, 65; treatment of, 63

I

Indican, tests for, 220

Indol, 221

Insomnia, vasomotor system and, 273

Intestinal antiseptics, 238

Intestinal intoxications, types of, 215, 225; treatment of, 237

Iodothylin, 5; effect of, on heart, 7; on liver, 8; on metabolism, 7

K

Kidney, internal secretion of, 42

Knoten, 244

L

Lactic-acid ferments, 239

Lactosuria, 171

Lehnhartz, treatment of gastric ulcer, 73

'Louping-ill,' 239

Lungs, œdema of, 281; vasomotor system and, 280

M

Mammary gland and its secretion, 35

Methæmoglobinæmia, 229

Microbic cyanosis, 229

Muscle extracts, 42

Myxœdema, 7

N

Nitrogen economy, 160

Nodal rhythm, 253

Novocaine, 26

Nutrient enemata, 67

O

œdema of lungs, 281; acute, 282

Orthostatic albuminuria, 150, 274

Ovarian extract, 34

Ovary, internal secretion of, 33

Oxalates, endogenous, 139; exogenous, 139

Oxaluria, 139

Oxybutyric acid, 189

P

Pancreas, influence on general metabolism, 103; safeguards against self-digestion of, 95

Pancreatic disease, manifestations of, 109

Pancreatic ferments, 100; in treatment of cancer, 115

Pancreatic glycosuria, 103, 176

Pancreatic inadequacy, 110, 113

Pancreatic infantilism, 93

Pancreatic reaction (Cambridge), 98, 114

Pancreatic secretion, 92; adaptation of, 110

Pancreatitis, 97, 99

Paralytic chorea, 225

Parathyroids, 11

Pentosuria, 171

Perigastric adhesions, 79

Phosphaturia, 144

Pituitary body, 41

Placenta, extract of, 35

344 PHYSIOLOGICAL PRINCIPLES

- Polycythæmia, cyanosis and, 301 ;
 relative, 310 ; splenomegalic,
 302
 Post-anæsthetic poisoning, 202,
 212
 Pressor nerves, 272
 Pulmonary circulation and the
 vasomotor system, 22, 280
 Pulsus alternans, 260
 Purin bodies, 123 ; endogenous,
 124 ; effects of, 126 ; estima-
 tion of, 129 ; exogenous, 124 ;
 fate of, 127 ; influence of drugs
 on, 133 ; significance of, 129
 Purinometer, 129
 Putrefactive bodies, intoxication
 by, 218
 Pyloric spasm, 56
 Pylorus, congenital hypertrophic
 stenosis of, 83
 Pyorrhœa alveolaris, intoxication
 from, 228
- R**
- Rectal feeding, 67
 Refractory period of heart, 247
 Rodagen, 13
- S**
- Sahli's test, 111
 Sauerin, 240
 Secretin, 92 ; in diabetes, 105
 Sino-auricular node, 245
 Spermin, 36
 Spleen and vasomotor system,
 275
 Splenomegalic polycythæmia, 302
 Staircase contractions of heart,
 247
 Steatorrhœa, 112
 Stokes-Adams disease, 250
 Stomach, dilatation of, 80 ; ex-
 amination of contents of, 88 ;
 glands of, 47 ; movements of,
 48
 Strontium salts, 330
 Strychnine in heart-block, 252,
 254 ; in heart-failure, 292
 Sulphæmoglobinæmia, 230
 Suprarenal capsules, 15
- T**
- Testis, internal secretion of, 36
 Thyminic acid (solurol), 134
 Thymus, 37 ; sudden death and,
 38
 Thyroidectin, 14
 Thyroid gland, 5 ; extract of, 7
 Thyrolytic serum, 14
 Tobacco, effect of, on blood-pres-
 sure, 297
- U**
- Urine, acetone in, 180, 188 ;
 albumin in, 149 ; diacetic acid
 in, 180 ; hæmatoporphyrin in,
 232, indican in, 220 ; oxalates
 in, 139 ; phosphates in, 144 ;
 purins in, 123 ; sugar in, 169
- V**
- Vaso-constrictor nerves, 270
 Vaso-dilator nerves, 270
 Vasomotor centre, 269
 Vasomotor system, 269 ; brain
 and, 276 ; heart and, 284 ; in-
 somnia and, 273 ; pulmonary
 circulation and, 280
 Vomiting, pernicious, in preg-
 nancy, 199, 211 ; recurrent, in
 children, 197, 210
- X**
- Xanthine, 121
- Y**
- 'Yahourth,' 239

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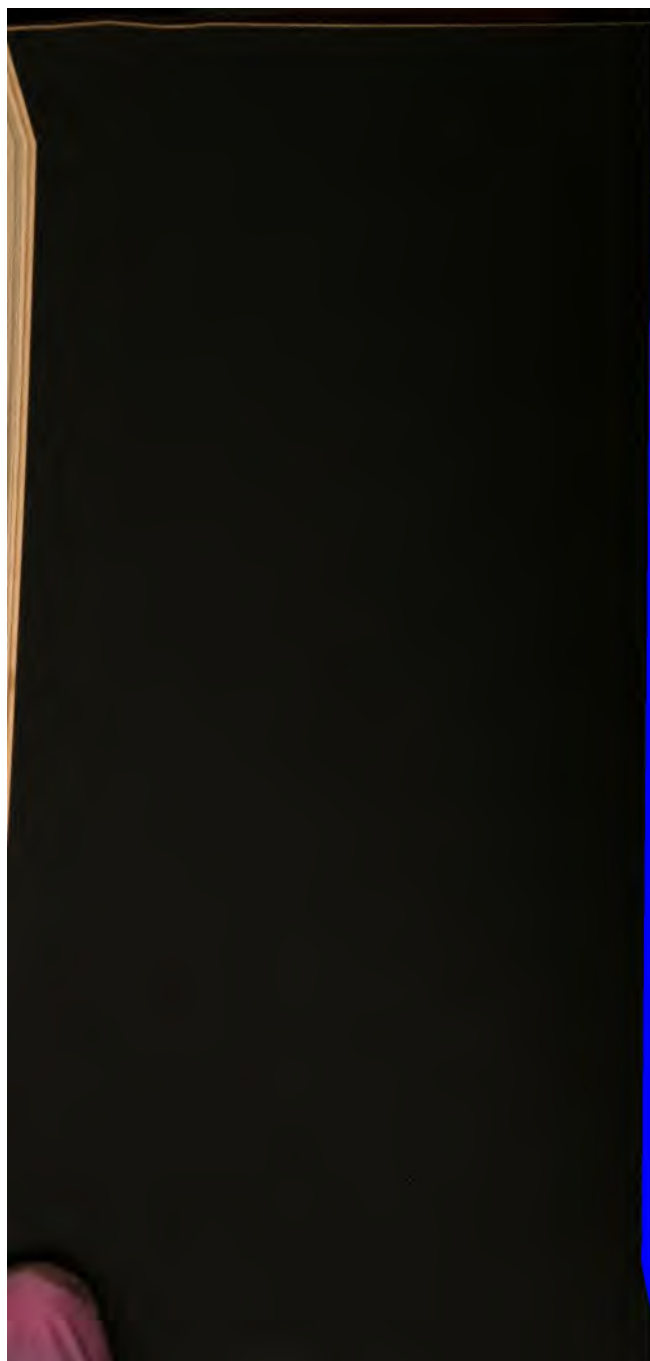
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